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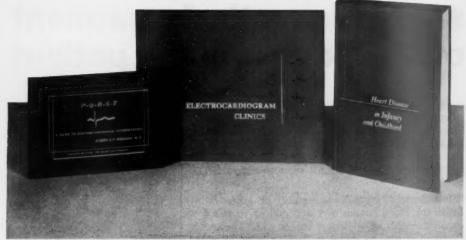
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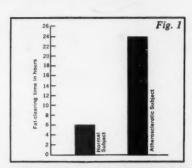
In figure #3, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

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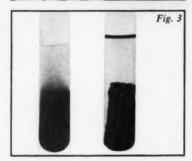
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References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. 45:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. 163:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959. 8. Fuller, H. L.: Circulation 20:699 (Oct.) 1959.

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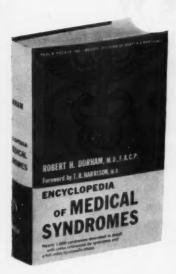
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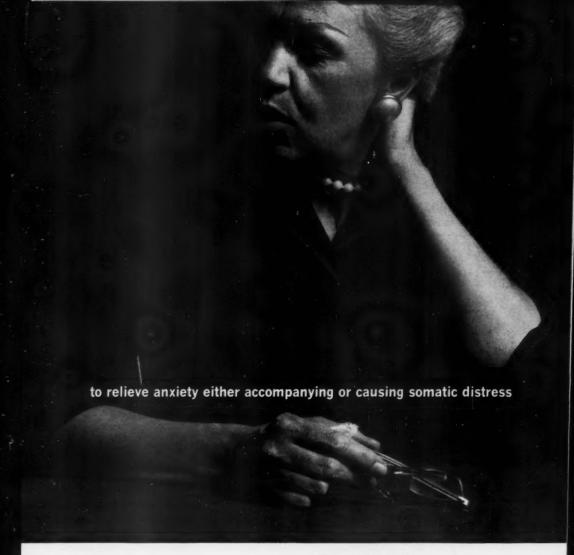
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Marx, F.J., in Triflnoperazine: Further Clinical and Laboratory Studies, Philadelphia, Lea & Febiger, 1959, p. 89.
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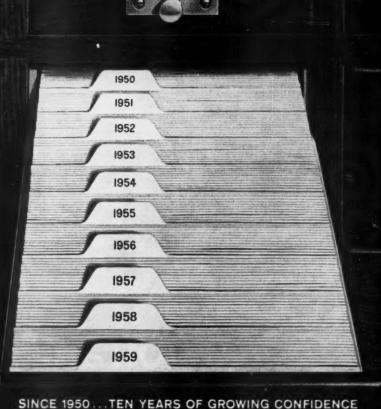
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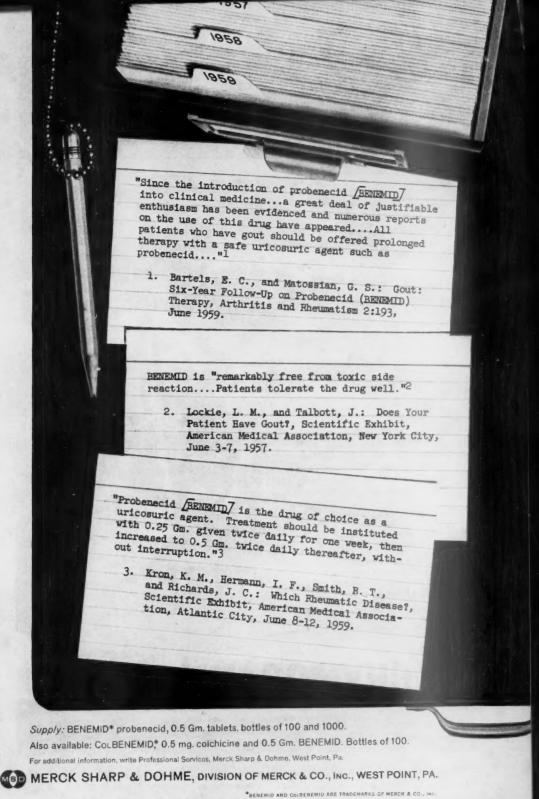
TO-451-60



SINCE 1950...TEN YEARS OF GROWING CONFIDENCE IN THE EFFECTIVENESS AND SAFETY OF







### CHYMORAL PRODUCED GOOD TO EXCELLENT RESULTS IN 77% OF CASES... WITH NO EVIDENCE OF TOXICITY OR SIDE EFFECTS14

condition	no. of cases	excellent/good	fair	no response
sinusitis and tonsillitis	18	14	2	2
asthma with or without bronchitis, emphysema	54	44	7	3
tracheo-bronchitis, bronchitis, bronchiectasis	31	21	7	3
TOTAL	103	79	16	8

#### CONTROLLED INFLAMMATION...LIQUEFIED VISCID MUCUS...RELIEVED DISCOMFORT

### Chymoral cuts healing time where inflammatory complications prolong the clinical course

Chymoral, a new ORAL antiinflammatory enzyme tablet formulated especially for intestinal absorption, prevents or reduces inflammation of all types through systemic action . . . normalizes inflamed mucosa of paranasal sinuses and trachealbronchial tract. Chymoral thins viscid bronchial and sinus secretions, facilitates raising of sputum, reduces amount of expectoration, makes for easier breathing. The recommended dose of 2 tablets q.i.d. assures the patient of 400,000 units of enzymatic activity daily. Each Chymoral tablet provides enzymatic activity equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. Bottles of 48 tablets.

1. Billow, B.W., et al.: Southwestern Med. 41:286, 1960.
2. Teltel, L. H., et al.: Indust. Med. 29:150, (April) 1960.
3. Taub, S. J.: Paper presented before the Annual Meeting, Pl Lambda Kappa Medical Fraternity, Mlami, Florida (March) 1980. 4. Clinical Reports to the Medical Dept., Armour Pharmaceutical Co., 1959.

in respiratory inflammation



CHYMORAL tabs#24

@ 1960, A. P. Co.

a pair of gynecologic patients:



both are free of pain-but only one is on

### **DILAUDID**.

(Dihydromorphinone HCI)

#### swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia before and after gynecologic, obstetric and surgical procedures. Its high therapeutic ratio is commonly reflected by lack of nausea and vomiting — and marked freedom from dizziness, somnolence, anorexia and constipation.

> ♠ by mouth ♠ by needle ♠ by rectum 2 mg., 3 mg., and 4 mg.

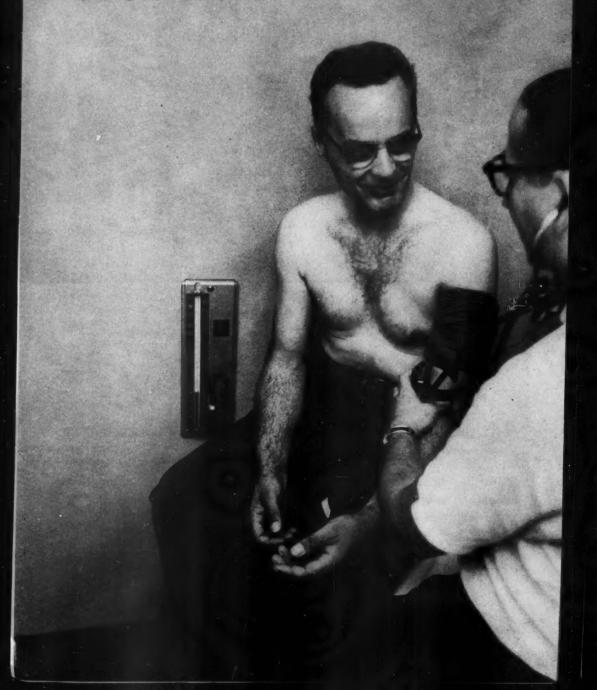
May be habit forming—usual precautions should be observed as with other opiate analgesics.



KNOLL PHARMACEUTICAL COMPANY · ORANGE, NEW JERSEY

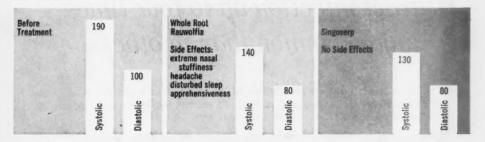
### this hypertensive patient prefers Singoserp

Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."



### ... and so does his physician

Clinician's report: J.M., a salesman, had a 16-year history of hypertension and was rejected by the U.S. Army because of high blood pressure. When treated with whole root rauwolfia, patient had satisfactory blood pressure response but could not tolerate side effects. Singoserp, in a dose of 0.5 mg. daily, not only reduced patient's blood pressure still further, but did not produce any side effects.



# Many hypertensive patients and their physicians prefer Singoserp<sup>®</sup> because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp Tablets, 1 mg. (white, scored). Also available: Singoserp®-Esidrix® Tablets #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® Tablets #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. Complete information sent on request.

Singoserp® (syrosingopine CIBA)
Singoserp®-Esidrix® (syrosingopine and hydrochlorothiazide CIBA)
a/admant



### AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE

## In what type of patient is urinary tract infection up to four times more common than in others?

The diabetic. Incidence of infections of the urinary tract in diabetes ranges from 12 to 20 per cent as compared to about 4.5 per cent for the rest of the population. *Source:* Peters, B. J.: J. Michigan M. Soc. 57:1419, 1958.

AMES



"In the presence of urinary infection the determination [of pH] is of the utmost utility. Often therapy is guided as much by the reaction of the urine as by the more detailed bacteriologic studies."

The detection of protein and the detection of sugar in the urine are two of the most commonly performed and diagnostically important tests in all types of medical practice.<sup>2</sup>

NOW...check urine reaction routinely— 3 test results in 10 seconds

COMBISTIX®

Colorimetric combination test for urinary pH, protein and glucose

- colorimetric readings eliminate guesswork...3 standardized color charts provided
- only drops of urine required . . . no more Q.N.S. reports
- · completely disposable...no "cleanup"
- no false positives from turbidity interference, drug metabolites or other urinary constituents

Supplied: COMBISTIX Reagent Strips - Bottles of 125.

(1) Williamson, P.: Practical Use of the Office Laboratory and X-Ray, Including the Electrocardiograph, St. Louis, C. V. Mosby Company, 1957, p. 41. (2) Free, A. H., and Fonner, D. E.: Studies With a Combination Test for Detection of Glucose and Protein, Abstract of 133rd Meeting, American Chemical Society, San Francisco, April 13-18, 1958, pp. 14c-15c.

protein

glucose



рН









In Ulcerative Colitis extensive clinical experience confirms

A Sulfidine 8
BRAND OF SALICYLAZOSULFAPYRIDINE

to be
a cornerstone
in today's management
of this distressing
disease.







Outstanding characteristics of Azulfidine treatment are

- Prompt remission of symptoms
- Bleeding and frequency of stools sharply reduced.
- Abdominal cramping controlled
- Rectal mucosa in many cases heals within a month
- Fever subsides, appetite improves
- · Can be given safely over long periods of time

Izulfidine is also a safe and effective drug in other forms of colitiand regional enteritis.



Pharmacia Laboratories, Inc.

501 Fifth Avenue, New York, 17., N.Y.

Film available on 'The Early Detection and Medical Management of Chronic Ulcerative Colitis', Address requests to Ideal Pictures for ASE Such Wager St. Chrone, III. in painful urinary infections
PYRIDIUM PERMITS PRECISE
CONTROL OF BOTH
PAIN AND PATHOGEN

PYRIDIUM
2 tablete T.I.D.
before meals
gour antibacterial
of choice,
Doctor

For the patient: FREEDOM FROM PAIN

Pyridium relieves pain, burning, urgency and frequency in 30 minutes. Unlike fixed urinary analgesic/antibacterial combinations, Pyridium analgesia can be continued as needed...stopped...or resumed if pain occurs.

For the physician: FREEDOM OF CHOICE

Freed from the restrictions of fixed analgesic/antibacterial combinations, the physician can choose the urinary antibacterial most specific for the infection. In making your choice of antibacterial, consider Mandelamine.

**PYRIDIUM** 

brand of phenylazo-diamino-pyridine HCI

stops urinary pain in 30 minutes



# in urinary infections MANDELAMINE PROVIDES BACTERIAL CONTROL WITHOUT RESISTANT MUTANTS



As resistance develops to more and more antibacterials, many physicians choose Mandelamine as their antibacterial of first choice in urinary infections. Mandelamine acts specifically in the urinary tract, and is effective against most urinary pathogens (including antibiotic-resistant Staph.). Resistant strains have not developed. Sensitization in any form has not occurred, even after prolonged use...and Mandelamine is economical, too.



## MANDELAMINE

brand of methenamine mandelate

the urine-specific antibacterial

### Blood pressure that goes up with stress often comes down with SERPASIL

One reason that many cases of hypertension respond to Serpasil is that many cases are associated with stress. Stress situations produce stimuli which pass through the sympathetic nerves, constricting blood vessels, and increasing heart rate. Hyperactivity of the sympathetic nervous system may elevate blood pressure; if prolonged, this may produce frank hypertension. By blocking the flow of excessive stimuli to the sympathetic nervous system, Serpasil guards against stress-induced vasoconstriction, brings blood pressure down slowly and gently.

In mild to moderate hypertension, Serpasil is basic therapy, effective alone "... in about 70 per cent of cases ... "\*

In severe hypertension, Serpasil is valuable as a primer. By adjusting the patient to the physiologic setting of lower pressure, it smooths the way for more potent antihypertensives.

In all grades of hypertension, Serpasil may be used as a background agent. By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

\*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.



## Independent Studies establish the effectiveness of **EKG** sol (1-3)

"The only difference that I could detect between the two products is that EKG SOL is more convenient to use." (1)

"---They are both equally ideal for routine studies." (2)

"No differences were noted between the electrocardiograms recorded with paste or cream.\*" (3) \*EKG sol

Economical, Convenient,
Pleasant for Patient
and Technician . . .

- Study conducted by M. A. Corrado, M. D., Georgetown University Hospital, Washington, D. C.
- Comparative study conducted by Aldo A. Luisada, M.D., The Chicago Medical School, Chicago, Ill.
- 3. C. A. Caceres, M. D. and George A. Kelser, Jr., M. D., A Comparison of Electrocardiograms Recorded With Cream\* and Paste, study conducted at George Washington University Hospital. (\*EKG sol)



# ENCOURAGING NEWS IN ANGINAL THERAPY

Reporting on extensive clinical trial of ISORDIL, a group of important investigators found "impressive improvement in 67% of patients...," favorable response in a total of 75%.

1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A. C.

In their thoroughly documented report on 60 angina patients studied by open clinical trial, Fisch, Boyle, Sperber, and DeGraff found improvement in 75% of patients; 18% did not respond. Minor side reactions (mostly headache) hindered evaluation in only 7% of the patients treated.

### Average Dosage Low, but Individualization Required

Average effective dose of ISORDIL was 10 mg. q.i.d.; 26% of patients received higher doses, 16% lower doses. Of all patients, 87% received and tolerated 5 to 15 mg. q.i.d.

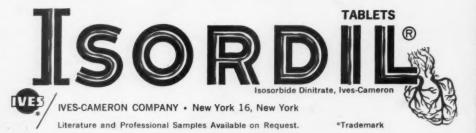
#### Headache Commonest Side Effect, Easily Relieved

Although headache occurred initially in 27% of patients studied, it caused discontinuance of ISORDIL in only 4 patients. Continued therapy, adjustment of dosage, or use of acetylsalicylic acid relieved headache in all other cases.

#### Other Studies Confirm Results, Establish Additional Benefits

Maintenance of active coronary vasodilatation by ISORDIL, as shown by Leslie,<sup>2</sup> Albert<sup>3</sup> and Fremont,<sup>4</sup> virtually eliminates periods of unprotection. Benefits are apparent as early as 15 minutes, persist for at least 4 hours. No lag in onset . . . important during early morning and postprandial stress.

References: 1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A.C.: Presented at the annual meeting of the American Therapeutic Society, Miami Beach, Florida, June 10, 1960. To be published. 2. Leslie, R.: Submitted for publication. 3. Albert, A.: In Manuscript. 4. Fremont, R.E.: To be published.





how does Mellaril differ from other potent tranquilizers?

## Mellaril

provides highly effective tranquilization, relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as jaundice



Parkinsonism blood dyscrasia dermatitis greater specificity of tranquilizing action results in fewer side effects



"A new phenothiazine derivative, thioridazine [Mellaril\*], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions....The response to treatment was considered satisfactory in 83.4 per cent of patients....In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."\*

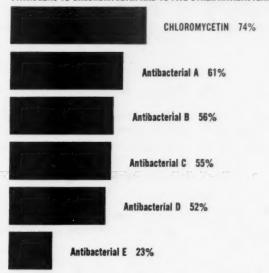
Supply: MELLARIL Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

\*David, N. A.; Logan, N. D., and Porter, G. A.; Evaluation of Thioridazine (Meliarii), a New Phenothiazine, in The Hospitalized Patient, A.M. & C.T. 7:364 (June) 1960.

# 4,860 CULTURES... 74% SENSITIVE TO CHLOROMYCETIN

(chloramphenicol, Parke-Davis)

IN VITRO SENSITIVITY OF 4,860 GRAM-POSITIVE AND GRAM-NEGATIVE
PATHOGENS TO CHLOROMYCETIN AND TO FIVE OTHER ANTIBACTERIALS\*



\*Adapted from Goodier, T. E. W., & Parry, W. R.: Lancet 1:356, 1959.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

PARKE, DAVIS & COMPANY · Detroit 32, Michigan

PARKE-DAVIS

# MER/29 reduces total body cholesterol in 8 out of 10 —and these are the patients most likely to benefit

#### your patient with high cholesterol levels...

MER/29 reduces both serum and tissue cholesterol, irrespective of diet. In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%. 1-4

#### your patient with angina pectoris...

concurrent benefits have been reported in some patients receiving MER/29. These include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin requirements, and an increased sense of well-being. 1,4,4-9

#### your patient with postmyocardial infarction . . .

while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "... reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."

#### your patient with generalized atherosclerosis...

atherosclerosis "... has been shown to afflict about 77% of American males as early as in the 20-to-30 age range." With MER/29 you have a new, well-tolerated means of lowering cholesterol—considered "... the sine qua non of the atheromatous lesion."

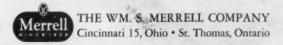
- compatible with other cardiovascular therapies: MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.
- safety data: Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.
- contraindication: Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

supplied: Bottles of 30 pearl gray capsules.

- ... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol
- ... no demonstrable interference with other vital biochemical processes reported to date
- ... convenient dosage: one 250 mg. capsule daily before breakfast
- ...toleration and absence of toxicity established by 2 years of clinical investigation

# MER/29

References: 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. 10:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. 18:428 (Mar.) 1959. 3. Oaks, W. W., et al.: A. M. A. Arch. Int. Med. 104:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. 2: (Suppl.) 618 (May) 1960. 5. Oaks, W. W.: Ibid., p. 612. 6. Hollander, W., et al.: Ibid., p. 637. 7. Halperin, M. H.: Ibid., p. 631. 8. Toro, J.: Ibid., p. 544. 9. Morrison, L. M.: J.A.M.A. 173:884 (June 25) 1960.





### extraordinarily effective diuretic."1

Efficacy and expanding clinical use are making Naturetin the diuretic of choice in edema and hypertension. It maintains a favorable urinary sodium-potassium excretion ratio, retains a balanced electrolyte pattern, and causes a relatively small increase in the urinary pH.2 More potent than other diuretics, Naturetin usually provides 18-hour diuretic action with just a single 5 mg. tablet per day - economical, once-a-day dosage for the patient. Naturetin & K - for added protection in those special conditions predisposing to hypokalemia and for patients on long-term therapy.

Supplied: Naturetin Tablets, 5 mg., scored, and 2.5 mg. Naturetin c K (5 c 500) Tablets, capsule-shaped, containing 5 mg. benzydroflumethiazide and 500 mg. potassium chloride. Naturetin č K (2.5 č 500) Tablets, capsule-shaped, containing 2.5 mg. benzydroflumethiazide and 500 mg. potassium chloride. For complete information consult package circular or write Professional Service Dept., Squibb, 745 Fifth Avenue, New York 22, N. Y. References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960, 2, Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

Naturetin Naturetin K



## OLD SALT

(or, How to chart a course to brighter diets in edema and hypertension)



Man, food and salt: a satisfying triumvirate. Yet the edema or heart patient may be denied this pleasant union every day. He eats, but without the bright touch salt brings. Small loss? Certainly. Still, small losses often loom large in the patient's mind. A good diuretic like Oretic can help out here. Oretic will successfully treat edema, and work well in mild to moderate hypertension. It produces a generous elimination of water and sodium. And this latter saluretic effect often opens the door to a more liberal low-sodium regime. Not every time, naturally. Each patient—each diet—is different. But an adjusted diet should be possible often enough to make the plan worth considering. Consider what it will mean to the patient to have the real pleasure of some real salt back on the table. You'll know how much it means, when he thanks you.

ORETIC (Hydrochlorothiazide, Abbott)



a potent means when the end is saluresis. Tablets, 25- and 50-mg.



#### in cholecystography . . . minimal PBI interference

For the Radiologist, excellence of visualization and low incidence of side effects<sup>1-10</sup> are two of the many advantages which have recommended Orabilex in cholecystography. For the Internist, Orabilex has been shown to cause the least interference with protein bound iodine levels of the commonly used cholecystographic contrast media. E. Fougera & Company, Inc., Hicksville, Long Island, N. Y.

#### Orabilex\* for more rapid return to normal PBI levels



References: 1. Teplick, J. G. et al: Am. J. Roentgenol. 80:961, Dec. 1958. 2. Tice, G. 1 Minsas Med. Soc. 60:118, March 1959. 3. Heacock, C. H. & Wilson, J. M.: Memphis M. J. 34:187, May 1959. 4. Whitchouse, W. & Fink, H. E., Jr.: Univ. of Michigan M. Bull. 32:218, July 1959. 5. Meszaros, W. T. & Rich, F. M.: J.A.M.A. 172:17, April 23, 1960. 6. Geffen, A.: Radiology 72:839, June 1959. 7. Van Epps, E. F. & Behlke, F. M.: J. I. Mowa Med. Soc., June 1959. 8. Bickham, C. E. Jr. et al: Southern Med. J. 53:77, Jan. 1960. 9. Morgan, L. A. & Parks, R. E.: Radiology 74:436, March 1960. 10. Reeves, R. J.: Am. J. Roentgenol. 83:5, May 1960. 11. Astwood, E. F.: Tr. Asin. Am. Phys. 70:183, 1957. 12. Shapiro, R. & Man, E. B.: J. A. M. A. 173:12, July 23, 1960.

# INCREASED LIFE EXPECTANCY FOR HYPERTENSIVES

"Life expectancy seems to be the one criterion that is most reliable and least questioned as a method of evaluating treatment for patients with elevated blood pressure." I "It is evident that effective therapy of hypertension will prolong the life of the patient by preventing the dreaded complications of this disease in the brain, the heart and the kidneys." "There is no doubt of the prolongation of life in group 3 and 4 (Keith-Wagener-Barker) by adequate antihypertensive treatment. Some authorities report a 50 per cent, five year survival ratio for treated patients with malignant hypertension as against a 1 per cent survival ratio for untreated patients."

Evaluation based on life expectancy is extremely difficult because of the peril of maintaining an untreated control group. The doctor, however, can evaluate the symptoms related to the elevated blood pressure.... We know that retinopathy may improve, the heart may be reduced in size, the electrocardiogram may improve and in favorable cases the blood urea nitrogen level may fall. These are reasonably objective criteria on which to base one's evaluation of treatment.

On the succeeding page is evidence that Unitensen included in any therapeutic regimen may improve the results in hypertension as measured by a regression of objective clinical changes in a substantial proportion of the patients treated.

Waldman, S., and Pelner, L.: Am. Pract. & Digest. Treat. 10:1139, 1959.
 Waldman, S., and Pelner, L.: Am. Pract. & Digest. Treat. 10:1139, 1959.
 Cohen, B. M.: paper presented at A.M.A. Convention, June, 1958.
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 Cohen, B. M.: Am. J. Cardiology 1:748, 1958.
 Kirkendall, W. J.: J. Iowa M. Soc. 47:300, 1957.
 Cherny, W. B., et al.: Obst. & Gynec. 9:515, 1957.
 Raber, P. A.: Illinois M. J. 108:171, 1955.
 McCall, M. L., et al.: Obst. & Gynec. 6:297, 1955.
 Finnerty, F. A.: Am. J. Med. 17:629, 1954.

Unlike diuretics or ganglionic blocking agents, Unitensen lowers blood pressure through widespread vasorelaxation. Normal vasomotor responses are not altered, and there is no venous pooling with resulting postural hypotension.<sup>3-5</sup> Through alleviation of cerebral vasospasm, Unitensen promotes cerebral blood flow and oxygen utilization.<sup>6-9</sup> Furthermore, Unitensen increases cardiac efficiency, improves renal function and tends to arrest the progress of vascular damage.<sup>3,4,10</sup>

Progress of Objective and Subjective Symptoms in Grades III and IV Hypertension Following Treatment with Unitensen and Unitensen-R

Observations in Patients' Treated up to 2 Years

Observations in Patients\* Treated up to 31/2 Years

The Course of Subjective Symptoms

Symptom	Number**	Improved	% Improved
Headache	27	21	77.7
Palpitation	20	13	65.0
Angina	15	9	60.0
Dyspnea	17	8	47.0

Number**	Improved	% Improved
43	38	88.0
29	19	65.5
21	16	76.0
27	14	51.0

Objective Changes Following Treatment

Finding	Number**	Improved	% Improved
Funduscopic Changes	41	24	58.5
Enlarged Heart	20	13	65.0
Abnormal EC	G 37	10	27.0
Proteinuria	31	12	38.7
Nitrogen Retention	17	6	35.2

Number**	Improved	% Improved
59	38	66.0
35	23	65.7
45	25	55.5
43	27	62.7
28	10	35.7

Left hand charts from Clinical Exhibit "The Ambulatory Patient with Hypertension" presented AMA Convention, San Francisco, June 22-27, 1958, by B. M. Cohen, M.D.

- \*All patients in this study were initially classified as Smithwick Grades III and IV.
- \*Expressed as the number of patients exhibiting the symptom recorded.

Right hand charts include patients previously reported who had been continuously maintained on Unitensen and Unitensen-R, plus additional patients later added to the study. From Clinical Exhibit "The Office Diagnosis and Treatment of the Patient with Hyperfension" presented American Academy of General Practice, Indianapolis, March 18-19, 1959, by B. M. Cohen, M.D.

#### UNITENSEN'

Each tablet contains: Cryptenamine (tannates) 2.0 mg.

#### UNITENSEN-PHEN®

Each tablet contains: Cryptenamine (tannates) 1.0 mg., Phenobarbital 15 mg.

#### UNITENSEN-R°

Each tablet contains: Cryptenamine (tannates) 1.0 mg., Reserpine 0.1 mg.

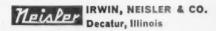
#### UNITENSEN° AQUEOUS

Each cc. contains: 2.0 mg. cryptenamine (acetates) in isotonic saline

new from Neisler

Analexin<sup>®</sup>

a new class of drug
for the relief of pain and muscle tension



#### In hypoprothrombinemia

# KONAKION

Rapid action

Wide margin of safety

Versatility of administration

Compatibility

Low dosage forms

rate of absorption faster than menadione or derivatives...more potent and lasting effects.

substantially safer than vitamin-K analogues-no kernicterus reported.

capsules for oral use...fine aqueous dispersion for parenteral administration.

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

no excess, no waste-packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired,

Capsules - 5 mg; Ampuls - 1 mg/0.5 cc



ROCHE LABORATORIES - Division of Hoffmann-La Roche Inc - Nutley 10, New Jersey

## in arthritis and allied disorders

## **Butazolidin**

Proved by a Decade of Experience Confirmed by 1700 Published Reports Attested by World-Wide Usage

Since its and sinflammatory processes yere first noted in Geigy laboraterer 10 sears ago, time and experience have seasily fortified the position of futuroloin as a leading nonhormonal inti-artintic agent, indicated in both prome and acute forms of arthritis, jutazolidin is noted for its striking iffectiveness in relieving pain, acreasing mobility and halting

Isutazolidin<sup>®</sup>, brand of phenylbutazone: red, sugar-coated tablets of 100 mg, sutazolidin<sup>®</sup> Alka: Grange and write apsules containing Butazolidin 100 mg, tried aluminum hydroxide gel 100 mg, agnesium trisificate 150 mg, comatropine methylbromide 1.25 mg.



for

liver impairment

associated with

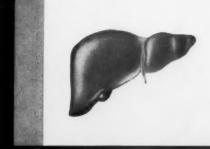
or aggravated by

alcoholism
diabetes
obesity
atherosclerosis
coronary disease

prescribe methischo

methionine • vitamin B<sub>12</sub> • choline • inositol • liver

the original complete lipotropic therapy



#### fatty livers, portal cirrhosis, and widespread liver damage,

with failure in detoxifying ability, and general hepatic dysfunction are commonly encountered in diabetes, obesity, alcoholism, atherosclerosis and coronary disease.

#### conversely, certain of these conditions tend to cause exacerbation of the hepatic disturbance,

thus creating a victous cycle seriously detrimental to the patient's health.

#### methischol helps terminate this vicious cycle

by increasing phospholipid turnover, reducing fatty deposits and fibrosis of the liver, stimulating regeneration of new liver cells, generally improving liver function.

#### when atherosclerosis and/or coronary disease occur

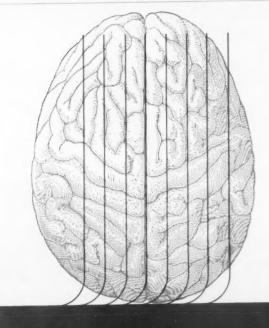
as they so frequently do in diabetes, alcoholism and obesity. Methischol aids in reducing elevated cholesterol levels, lowering chylomicron-lipomicron ratios towards the normal, and improving cholesterol and fat transport and metabolism.

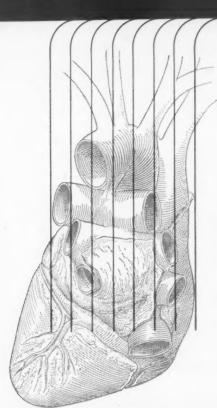
#### methischol

capsules bottles of 100, 250, 500 and 1000. syrup bottles of 16 for samples and detailed literature write

#### u. s. vitamin corporation

Arlington Funk Laboratories, division 250 East 43rd St. New York 17, N. Y.





#### To lift depression

Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.

Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, e.g., was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.6

A single agent, with two distinct primary effects, for two important clinical indications

# Marpiane of potency/safety

#### To control pain in "difficult" cases of angina pectoris

Marplan prevents anginal pain, 1-3 increases exercise tolerance 2.4.5 and reduces nitroglycerin requirements, 2.3 It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.

Marplan improves the mental climate: Not only could anginal patients placed on Marplan "...do more than formerly..." but they also felt better, were more alert, more cheerful. Late 1 The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

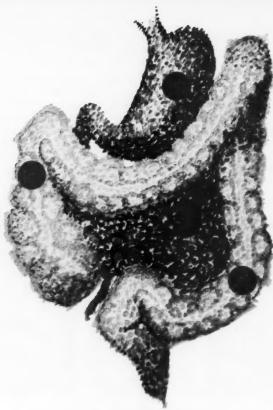
Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

Consult literature and dosage instructions, available on request, before prescribing.

Selected bibliography from 38 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399, 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, Virginia M. Month., 87:23, 1960. 4. C. C. Griffith, Clin. Med., 6:1555, 1959. S. G. C. Griffith, Dis. Nerv. System, 21: (Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, Dis. Nerv. System, 20: (Suppl.), 26, 1959.

MARPLAN® - 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine





for peptic ulcer...

for gastrointestinal disorders, specify

# **SUSTAGEN**

COMPLETE THERAPEUTIC NUTRIMENT

#### to help restore and maintain good nutrition

#### in peptic ulcer

Sustagen "...systematically enhances healing of the ulcer and restoration of the patient to a state of optimal nutrition."

#### in ulcerative colitis

"...high protein, high carbohydrate, high caloric, low residue diet" imperative. Sustagen provides this diet.

#### provides all essential nutrients

Sustagen may be used as the sole source of food or to fortify the diet—helps build and repair tissue, restore nitrogen balance, enhance rehabilitation,

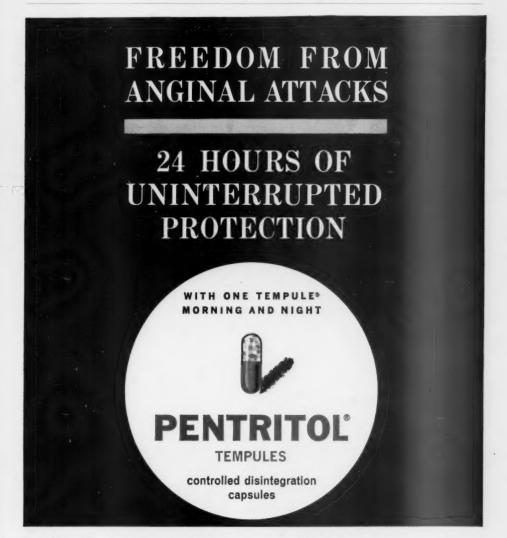
#### orally-or by tube

Palatable,<sup>3</sup> easy to take in beverage form—just one glass provides 390 calories and 23.5 Gm. protein. In tube feeding Sustagen alone provides complete nutrition. Mixes and flows readily. Bland, low in bulk, low in fiber, it is well tolerated—easy to use, easy to take.

#### References:

(1) Winkelstein, A.: Am. J. Gastroenterol. 27:45-52 (Jan.) 1957. (2) Brown, C. H.: Am. Pract. & Digest Treat. 9:405-411 (March) 1958. (3) Winkelstein, A., and Schweiger, E.: J.A.M.A. 160:1111-1113 (March 31) 1956.





The best has been improved. PETN, proven over the years to be the most effective drug for preventing anginal attacks, has been improved by incorporating it into controlled disintegration capsules. Pentritol Tempules exhibit the benefits of PETN "... plus a smooth sustained clinical result that seemed to show a superior effect."

Pentritol Tempules given every 12 hours reduced or eliminated nitroglycerin requirements, stopped anginal attacks or reduced their frequency, eliminated or mitigated pain, and increased the capacity for physical activity. Patients previously taking PETN in tablets with little progress, responded favorably to Pentritol Tempules.<sup>2</sup>

Recommended dose is 1 Pentritol Tempule morning and evening, approximately 12 hours apart. Available in bottles of 60 Tempules. Also available: Pentritol-B Tempules with 50 mg. of butabarbital added for vasodilation *plus* sedation.

1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

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ARMOUR PHARMACEUTICAL COMPANY . KANKAKEE, ILLINOIS Armour Means Protection

another patient with hypertension?



indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES

HYDRO DIURIL with RESERPINE

#### HYDROPRES can be used:

- alone (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- as basic therapy, adding other drugs if necessary (should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- as replacement therapy, in patients now treated with other drugs (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

#### **HYDROPRES-25**

25 mg. HydroDIURIL, 0.125 mg. reserpine. One tablet one to four times a day.

#### HYDROPRES-50

50 mg. HydroDIURIL, 0.125 mg. reserpine. One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

OHYDROPRES AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

### **NOW...**FOR ACUTE AND CHRONIC ARTHRITICS

# More complete freedom from pain with reduced steroid dosage

PAIN EASES, MUSCLES RELAX WITH SOMA® INFLAMMATION SUBSIDES WITH PREDNISOLONE

WHEN PAINFUL MUSCLES RELAX, INFLAMED JOINTS NEED LESS STEROID



USUAL DOSAGE: One or two SOMAcort Tablets four times daily. SUPPLIED: As white, scored tablets, each containing 350 mg. SOMA (carisoprodol) and 2 mg. prednisolone; bottles of 50.

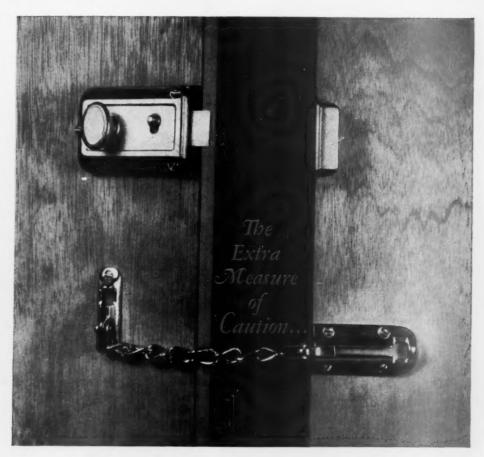
# SOMAcort

ANTI-INFLAMMATORY / MUSCLE RELAXANT / ANALGESIC



WALLACE LABORATORIES, Cranbury, N. J.

Literature and samples on request.



#### Tetracycline now combined with the new, more active antifungal antibiotic-Fungizone-for broad spectrum therapy/antimonilial prophylaxis

A new advance in broad spectrum antibiotic therapy, MYSTECLIN-F provides all the well-known benefits of tetracycline and also contains the new, clinically proved antifungal antibiotic, Fungizone. This Squibb-developed antibiotic, which is unusually free of side effects on oral administration when given in oral prophylactic doses, has substantially greater in vitro activity than nystatin against strains of Candida (Monilia) albicans.

Thus, in addition to providing highly effective broad spectrum therapy, MYSTECLIN-F prevents the monilial overgrowth in the gastrointestinal tract so commonly associated with such therapy. It helps to protect the patient from troublesome, even serious, monilial complications.

New Mysteclin-F provides this added antifungal protection at little increased cost to your patients over ordinary tetracycline preparations.

Arailable as: MYSTECLIN-F CAPSULES (250 mg./50 mg.) MYSTECLIN-F HALF STRENGTH CAPSULES (125 mg./25 mg.) MYSTECLIN-F FOR SYRUP (125 mg./25 mg. per 5 cc.) MYSTECLIN-F FOR AQUEOUS DROPS (100 mg./20 mg. per cc.)

For complete information, consult package insert or write to Professional Service Department, Squibb, 745 Fifth Avenue, N. Y. 22, N. Y.

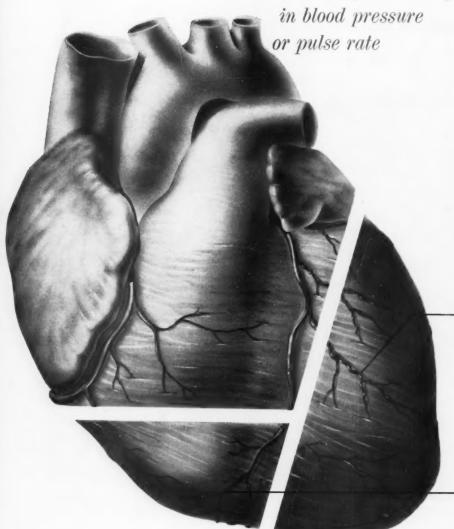
MYSTECLIN-F

Squibb Phosphate-Potentiated Tetracycline (SUMYCIN) plus Amphotericin B (FUNGIZONE)

SQUIBB Squibb Quality -

THISTECLIN'S, ISUMYCIN'S AND INJURGICANC AND SQUIRE TRACEMARKS

improve coronary
blood flow with
no significant change
in blood pressure
or pulse rate



#### In angina pectoris, the

gradual, prolonged action of Peritrate avoids significant drop in blood pressure, increase in pulse rate, and typical nitrate headache. Peritrate reduces frequency and severity of anginal attacks in 4 out of 5 patients, increases exercise tolerance, reduces nitroglycerin dependence, improves ECG findings.

In postcoronary management, gradual, prolonged action helps establish and sustain collateral circulation safely, to reduce the extent of myocardial damage, support natural healing and repair, and minimize any ensuing anginal attacks.

basic in coronary artery disease

brand of pentaerythritol tetranitrate



NEW form available: Peritrate with Phenobarbital Sustained Action.

1 tablet on arising and 1 tablet 12 hours later.

# PREMARINS WITH MEPROBAMATE

# 400

### FOR PROVEN MENOPAUSAL BENEFITS

The vast majority of menopausal women, especially on the first visit, are nervous, apprehensive, and tense. PMB-200 or PMB-400 gives your patient the advantage of extra relief from anxiety and tension, particularly when the patient is "high strung," under prolonged emotional stress, or when psy-

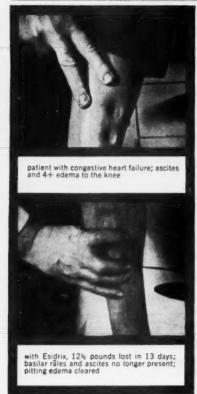


chogenic manifestations are acute. Proven menopausal benefits are confirmed by the wide clinical acceptance of "Premarin," specifically for the relief of hot flushes and other symptoms of estrogen deficiency, together with the well established tranquilizing efficacy of meprobamate.

Two potencies that will meet the needs of your patients: PMB-200 — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe PMB-400 — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

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benefits
in edema,
benefits in
hypertension
plus built-in
potassium
protection

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# NEW ESIDRIX-K

New ESIDRIX-K provides all the oral diuretic-antihypertensive advantages of ESIDRIX, plus a generous potassium supplement. ESIDRIX produces marked excretion of salt and water in edematous patients, and in many hypertensive patients significantly reduces blood pressure, alone or with other antihypertensive drugs. Potassium excretion is minimal, and the built-in K supplement further helps eliminate problems due to potassium loss. Three ESIDRIX-K tablets provide potassium equivalent to one quart of fresh orange juice; ESIDRIX-K is coated to prevent gastric irritation.

Complete information sent on request.

Supplied: Esidrix-K <u>Tablets</u> (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

Esidrix-K is especially indicated for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt-restricted diets.

C I B A



Gaining the cooperation of your patient is the hardest part in most reducing programs. PET *Instant* Nonfat Dry Milk helps you meet that problem in these ways:

PET Instant instead of whole milk for drinking cuts calories in half. Yet it supplies all the essential milk nourishment, except the fat. Used in cooking, it allows the diet to include many foods not permissible when made with whole milk or cream.

Since nonfat milk is the richest source of high-quality protein among the common foods, PET *Instant* helps combat fatigue and create a feeling of satisfaction.

PET *Instant* is a delicious, fresh-tasting beverage—one your patients will enjoy using. It mixes instantly ... costs only about 8¢ a quart.



Instantized so it dissolves almost at the touch of water.

All the protein, calcium and B-vitamins of whole milk without the fat



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In listless and lethargic overweight patients, 'Dexedrine' assures both a gentle stimulation that encourages normal physical activity and a positive, physiologic control of appetite.

'Dexedrine' Tablets (5 mg.), 30 to 60 minutes before meals, are particularly effective in patients who overindulge at meals.

'Dexedrine' Spansule® sustained release capsules (5 mg., 10 mg., or 15 mg.), taken in the morning, are particularly effective in patients who overeat both at and between meals.

For the listless and lethargic overweight patient, there is no more effective treatment than

her DOCTOR
her DIET

SMITH
NUNES
FRENCH

and DEXEDRINE

brand of doutes amplitudemine sulfate.

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## Leukemia ....

# **'LEUKERAN'**....

CHLORAMBUCIL (formerly known as C. B. 1348)

#### FOR CHRONIC LYMPHOCYTIC LEUKEMIA

A derivative of nitrogen mustard, it has provided amelioration of follicular lymphoma, lymphocytic lymphoma with or without leukemia, and Hodgkin's disease.

Sugar-coated Tablets of 2 mg.

## 'MYLERAN'

#### **BUSULFAN**

#### FOR CHRONIC MYELOCYTIC LEUKEMIA

'Myleran' has been reported to induce remissions, lasting up to two years, in chronic myelocytic leukemia. In addition to the decrease in total white cell count and a selective reduction of immature myeloid cells, it usually gives, early after its administration, a rise in hemoglobin level and pronounced subjective improvement.

Tablets of 2 mg.

## 'PURINETHOL'

#### **MERCAPTOPURINE**

#### FOR ACUTE LEUKEMIA AND CHRONIC MYELOCYTIC LEUKEMIA

'Purinethol' provides worth-while temporary remissions, either partial or complete, in a high percentage of patients. In general, a higher proportion of children than adults with acute leukemia respond favorably.

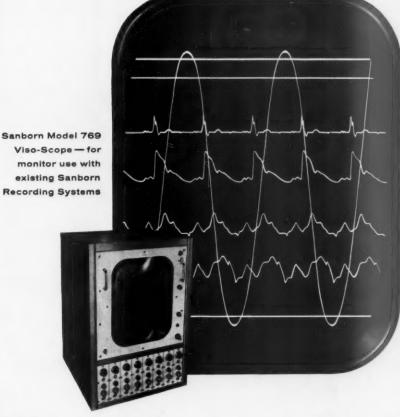
Tablets of 50 mg.

Facilities for complete and frequent blood counts must be available for patients receiving 'Leukeran', 'Myleran' or 'Purinethol'.

Full information about these products will be sent on request.



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoo, New York



# 8 EVENTS AT ONCE . . . ON A 17 INCH SCREEN

THE vertically mounted 17° screen provides ample space for up to 8 clear, long-persistance traces to be shown simultaneously on the Sanborn Model 769 Viso-Scope. Individual plug-in gating amplifiers in the 769 perform the function of an electronic switch—one amplifier for each signal to be shown on the 'scope—the signals being derived by direct connection of the 769 to existing Sanborn Recording Systems such as Model 60 Twin-Viso, Models 64, 77M, 150M and 350M Poly-Visos, and 550M Poly-Beam.

Automatic or manual trace sweep speeds of 2, 4 and 8 seconds (5, 2.5, and 1.25 inches/sec) are provided and an additional manual sweep speed of 25 seconds is included for use when slowly changing waveforms such as dye dilution curves are studied.

Controls permit sensitivity ranges from 5"/volt to \%" per volt, positioning of each signal at any level

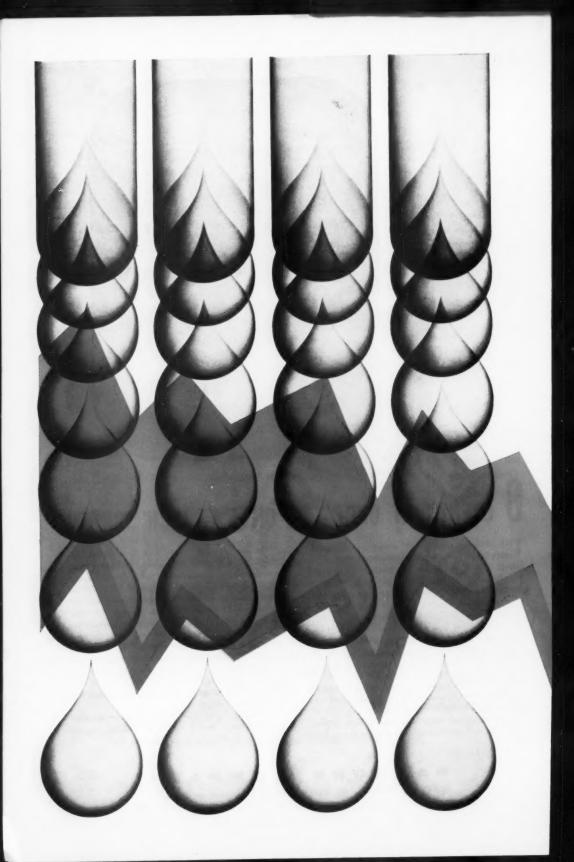
on the screen, and vector loop presentation. A Polaroid filter is used to minimize interference from room lighting, and provision is made for tilting the 'scope unit forward (up to 20 degrees) for optimum viewing ease. Front and rear input connections are available. With suitable cabling, several 769 units can be connected together for master slave operation.

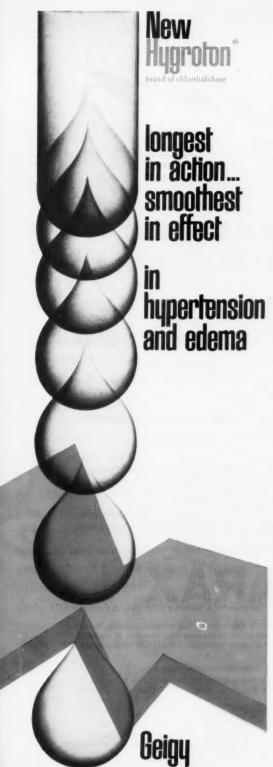
The Model 769 Viso-Scope — scheduled for delivery starting in September — is the first of a group of Sanborn "760" Monitor Units (including low voltage preamplifiers) soon to be made available for use in Hospital Operating Rooms, Recovery Rooms and Intensive Care Units, and by Catheterization Units and Teaching Groups.

For complete details, contact your nearest Sanborn Branch Office or Service Agency, or write the Inquiry Director at the Main Office in Waltham.



MEDICAL DIVISION, 175 WYMAN STREET, WALTHAM 54, MASS.





potent antihypertensive-saluretic

greater loss of sodium lesser loss of potassium

A new antihypertensive-saluretic, Hygroton now enables still more effective and safer control of hypertension and edema.

more evenly sustained therapeutic response Because it has the most prolonged action of all diuretics1 Hygroton exercises smoother, more evenly sustained therapeutic effect ... with almost complete freedom from significant side reactions. 2-4

more nearly pure natriuretic effect Hygroton produces only minimal potassium loss1,5 . affords a better sodium-potassium ratio than other saluretics.5

more liberal diet for the patient As a rule, with Hygroton restriction of dietary salt is unnecessary.

more convenience and economy Administration of just three single doses per week, for maintenance therapy, made feasible by the prolonged action of Hygroton,<sup>2</sup> insures maximal convenience and economy.

affording still greater assurance of response

In arterial hypertension sustained control without side reactions.

In the management of arterial hypertension Hygroton produces significant and sustained fall in blood pressure in 83 per cent of patients without production of autonomic side effects.6 Comparatively it affords "superior overall clinical effect" to that of other commonly used diuretics.

In edematous states copious diuresis without electrolyte imbalance.

In edema associated with congestive failure, nephrosis, hepatic cirrhosis, pregnancy or hypercortisonism Hygroton produces a marked salt and water diuresis without significant effect on other electrolytes.<sup>2-5</sup> Edematous swelling, dyspnea, cough and other symptoms are dramatically relieved.

More detailed information available on request.

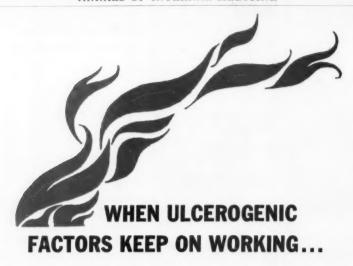
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1. Stenger, E. G. et al.: Schweiz. med. Wchnschr. 89:1126, 1599. 2. Fuchs, M. et al.: Current Therap. Research 2:11, Jan. 1960. 3. Reutter, E and Schaub, E: Schweiz. med. Wchnschr. 89:1138, 1959. 4. Veyrat, R. et al.: Schweiz med. Wchnschr. 89:1133, 1959. 5. Ford, R. V. Wanuscript submitted for publication. 6. Analysis of Case Reports Compiled by Biostatistical Dept. of Geigy Pharmaceuticals. 7. Bryant, J. M.: Report to Geigy Pharmaceuticals.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.



Geiny, Ardsley, New York

HY 236-60





Think of your patient with peptic ulcer—or G.I. dysfunction—on a typical day. Think of the anxieties, the tensions.

Think, too, of the night: the state of his stomach emptied of food.

Then think of ENARAX. For ENARAX was formulated to help you control precisely this clinical picture. ENARAX provides oxyphencyclimine, the inherently long-acting anticholinergic (up to 9 hours of actual achlorhydria!)... plus Atarax, the tranquilizer that doesn't stimulate gastric secretion.

Thus, with b.i.d. dosage, you provide continuous antisecretory/antispasmodic action and safely alleviate anxiety . . . with these results: ENARAX has been proved effective in 92% of G.I. patients.<sup>2-4</sup>

When ulcerogenic factors seem to work against you, let ENARAX work for you.



(10 MG. OXYPHENCYCLIMINE PLUS 25 MG. ATARAX\*) A SENTRY FOR THE G.I. TRACT

dosage: Begin with one-half tablet b.i.d.—preferably in the morning and before retiring. Increase dosage to one tablet b.i.d. if necessary, and adjust maintenance dose according to therapeutic response. Use with caution in patients with prostatic hypertrophy and only with ophthalmological supervision in glaucoma.

supplied: In bottles of 60 black-and-white scored tablets. Prescription only.

References: 1. Steigmann, F., et al.: Am. J. Gastroenterol. 33:109 (Jan.) 1960. 2. Hock, C. W.: to be published. 3. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 4. Data in Roerig Medical Department Files.

FOR HEMATOPOIETIC STIMULATION WHERE OCCULT BLEEDING IS PRESENT HEPTUNA PLUS

THE COMPLETE ANEMIA THERAPY

Disturbing?



New York 17, N. Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being™

### they help the cough remove its cause

These elegant antitussives comprise a group of significantly superior expectorants from which you may select the formula best suited for your coughing patient.

First of all, they have more in common than mere delectability to eye and palate: they all include glyceryl guaiacolate. This remarkable expectorant aids the coughing mechanism by increasing the secretion of Respiratory Tract Fluid, which helps liquefy sputum, 1,3 makes bronchial and tracheal cilia more efficient, 1,2 and acts as a demulcent. 1,3-5 Through its effects, all four expectorants promote the natural purpose of the cough, which is to remove the irritants that cause it.1,2

In addition, the Robins antitussive armamentarium provides a choice of widely accepted drugs in various combinations with glyceryl guaiacolate for treating different kinds of coughs and associated symptoms. For antihistaminic effects, there is Dimetane® or prophenpyridamine; for bronchodilation and nasal decongestion, there are sympathomimetic agents; and for suppression of the "too frequent" cough, there is codeine or dihydrocodeinone.

Each teaspoonful contains: Glyceryl guaiacolate. 100 mg.

Each teaspoonful contains: Glyceryl guaiacolate... Prophenpyridamine maleate... 7.5 mg. Codeine phosphate..

# Dimetane<sup>®</sup>

(exempt narcotic)

Each teaspoonful contains: Parabromdylamine maleate (DIMETANE) .. 2 mg. Glyceryl guaiacolate... 100 mg. Phenylephrine HCl, USP.. 5 mg. Phenylpropanolamine HCl, 5 mg.

Each teaspoonful contains the Dimetane Expectorant formula plus Dihydrocodeinone bitartrate, NF. 1.8 mg. (exempt narcotic)

References: 1. Cass, L. J., and Frederik, W. S.: Am. Pract. & Digest Treat. 2:844, 1951. 2. Blanchard, K., and Ford, R. A.: Journal-Lancet 74:443, 1954. 3. Hayes, E. W., and Jacobs, L. S.: Dis. Chest 30:441, 1956. 4. Blanchard, K., and Ford, R. A.: Rocky Mountain M. J., Vol. 52, No. 3, 1955. 5. Boyd, E. M., and Pearson: Am. J. M. Sc. 211:602, 1946. A. M. ROBINS COMPANY, INC., RICHMOND 20, VIRGINIA





# for every phase of cough... comprehensive relief

# AMBENYL EXPECTORANT

AMBENYL EXPECTORANT quickly comforts the coughing patient because it is formulated to relieve all phases of cough due to upper respiratory infections or allergies. Combining Ambodryl®—potent antihistaminic; Benadryl®—the time-tested antihistaminic-antispasmodic; and three well-recognized antitussive agents, AMBENYL EXPECTORANT:

soothes irritation • quiets the cough reflex
 decongests nasal mucosa • facilitates expectoration • decreases bronchial spasm • and tastes good, too.

Each fluidounce of AMBENYL EXPECTORANT & contains:
Ambodryl® hydrochloride
Benadryl® hydrochloride
Dihydrocodeinone bitartrate 1/6 gr.
Ammonium chloride 8 gr.
Potassium guaiacolsulfonate 8 gr.
Menthol q.s.
Alcohol

Supplied: Bottles of 16 ounces and 1 gallon.

Dosage: Every three or four hours—adults, 1 to 2 teaspoonfuls; children ½ to 1 teaspoonful.

& Exempt narcotic

PARKE, DAVIS & COMPANY Detroit 32, Michigan

PARKE-DAVIS

# RONCOVITE\*MF IS RAPIDLY BECOMING THE DRUG OF CHOICE IN ANTI-ANEMIA THERAPY...

#### because...

Cobalt is the only clinically proved the rapeutic agent which enhances the formation of erythropoietin, the hormone which regulates erythropoies is in the body.  $^{1\cdot3}$ 

#### because...

Roncovite through the effect of Cobalt-enhanced erythropoietin improves iron utilization by activating this normal physiologic process.  $^{3\cdot4}$ 

#### because...

The result is a more rapid and complete hematologic response in the anemic patient  $\dots^{5\cdot 9}$ 

#### and because...

The safety of Roncovite has been thoroughly attested in published literature and demonstrated during the administration of over 365 million doses.  $^{6,10,11}$ 

1. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. P.: Blood 13:55 (Jan.) 1958. 2. Murdock, H. R. Jr.: Am. Pharm. Assoc. (Sci. Ed.) 48:140, 1959. 3. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science 125:1085 (May 31) 1957. 4. Center, W. M.: Clin. Med. 7:713 (April) 1960. 5. Holly, R. O.: Obst. & Gynec. 9:299 (Mar.) 1957. 6. Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1956. 7. Flynn, R. T.: Therapy with Cobalt and Iron for Correction of Anemia in Pregnancy, Presented at Michigan and Wayne Co. Acad. GP. Postgrad. Clinic, Detroit, Mich., Nov. 11-12, 1959. 8. Tevetoglu, F., and Ozkaragoz, K.: M. Times 86:81 (Jan.) 1958. 9. Craig, P. E.: Clin. Med. 6:597 (April) 1959. 10. Hill, J. Mr.; LaJous, J., and Sebastian, F. J.: Cobalt Therapy in Anemia, Texas J. Med. 51:686 (Oct.) 1955. 11. Tevetoglu, F.: J. Pediat. 49:46 (July) 1956.

Please write for monograph,
"The Hormone Erythropoietin."
Roncovite literature also
available on request.

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO

### Helps you take the misery out of menopause

as hormones alone often don't do



### Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Desage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: Milprem-400, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Milprem-200, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

(Miltown® plus natural estrogens)

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

## in edema or

- more doctors are prescribing –
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"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., 59:1769, (May 1) 1959.



"... our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.



"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., 169:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg, tablets DIURIL once or twice a day. Hypertension—One 250 mg, tablet DIURIL twice a day to one 500 mg, tablet DIURIL three times a day.

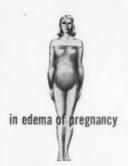
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in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.



"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



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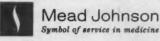
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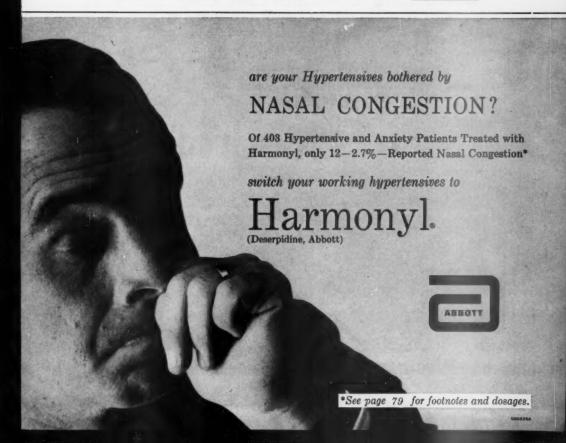
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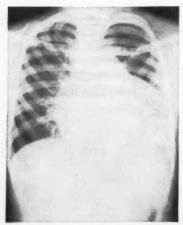
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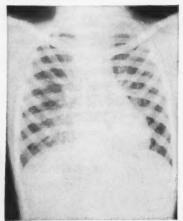


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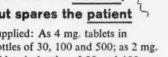
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<sup>1.</sup> Massell, B. F.: Paper presented at A Symposium on Steroid Therapy, Chicago, Ill., May 15-16, 1959.

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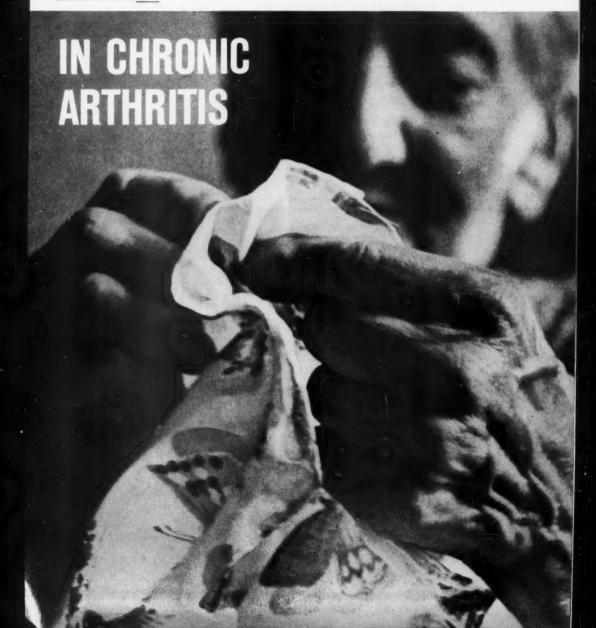
Robinson, W. D. Report to A. M. A. Council on Foods and Nutrition, <u>J. A. M. A.</u> 188:253 (Jan. 18) 1958.
 Spies, T. D.: J. A. M. A. 107:675 (June 7) 1956.

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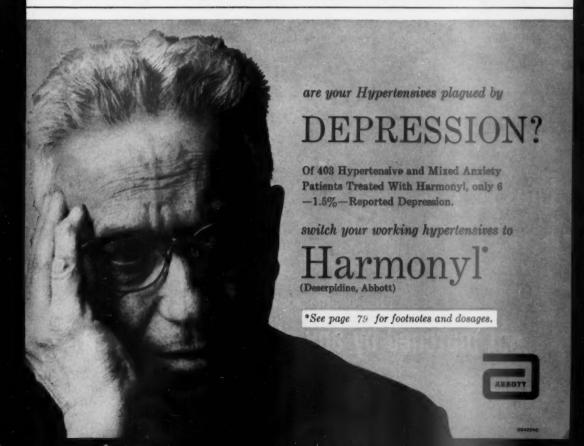
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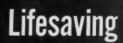


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Miller, A. J., and Moser, E. A.: J.A.M. A. 169:2000, April 25, 195

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- Billow, B.W. et al, The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
   Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April 1050

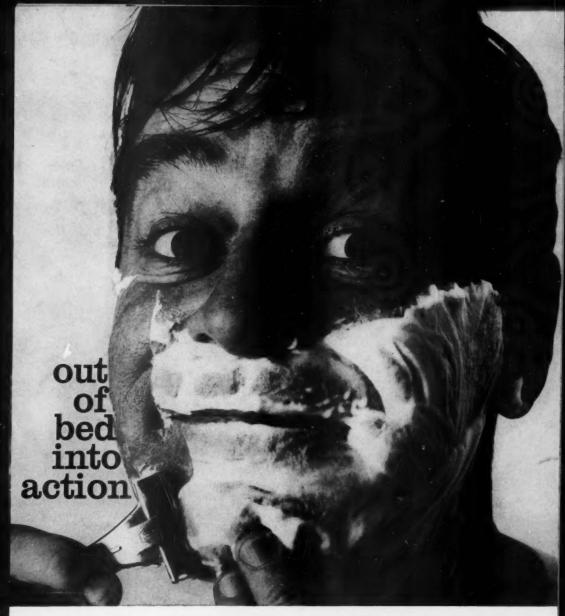
- Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.

  3. Rawls, W.B. and Evans, W.L. Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N.Y. J. Med., 59:1774, May, 1959.

  4. Frohman, I.P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, An Alkaloid of Rauwolfa Canescens, Med. Ann. District of Columbia, 27:641, December, 1958.

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\*Newcomer, V. D., et al.: A.M.A. J. Dis. Child. 99:585, 1960.

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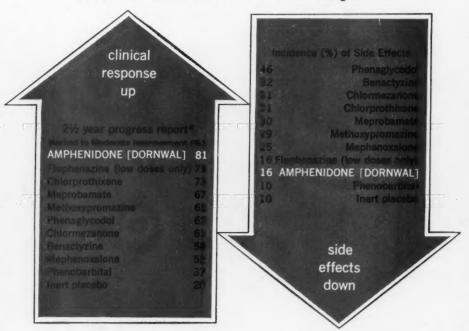
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\*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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\*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec.19) 1959. \*Continuous via Augustia Squibb Quality-the

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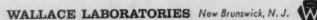
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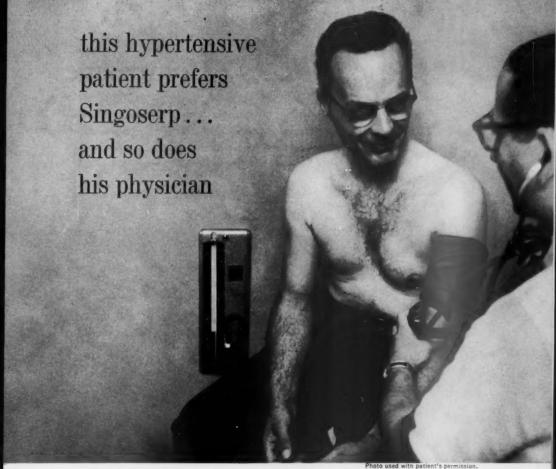
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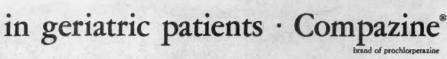
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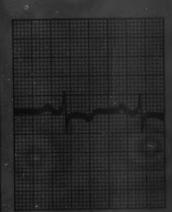
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Fuchs, M.: A review of the thiazide pharmacology, Paper presented at Puerto Rican M. Soc., San Juan, Puerto Rico, Jan., 1960.

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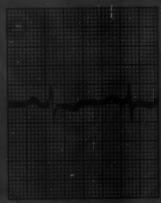


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#### References.

2. Alfaro, R. D.; Gracasia, V. and Schwater, E.; Elchieses Acad. Con., Pract., Detroit, November, 1989. S. Bush, G.; Michigan Acad. Gen., Pract., Symposium, Detroit, 1969. S. Harwits, E.; Personal communication, 1989. d. Spielman, A. R.; Michigan Acad. Gen., Pract. Symposium, Detroit, 1989. B. Bavets, E.; Michigan Acad. Gen., Pract. Symposium, Detroit, 2008. G. Decina, L. J.; Exper. Med. & Surg. in press. 7, E. anian, J. S.; Personal communication, 1989. B. Kreen and Storchi Personal communication, 1989.

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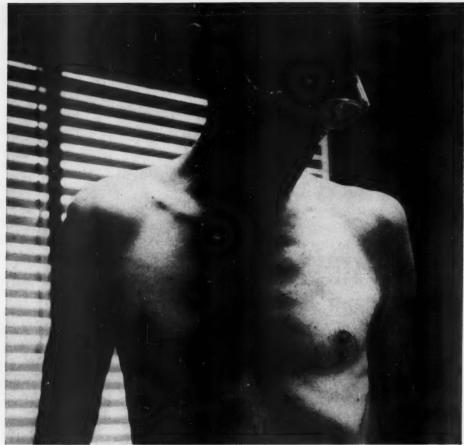
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congestive heart failure

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VOLUME 53

**OCTOBER**, 1960

NUMBER 4

This issue of the

### ANNALS OF INTERNAL MEDICINE

is dedicated to

MAURICE C. PINCOFFS, M.D., M.A.C.P.

Editor, 1933-1960



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#### A Tribute

October of this year marks the retirement of a man who has become a legend in the history of The American College of Physicians. After 27 years of dedicated service as Editor of the Annals of Internal Medicine, Dr. Maurice C. Pincoffs, distinguished and revered Master of the College, has indicated his desire to be relieved of the arduous responsibilities that have proved him to be a brilliant physician, a scholarly gentleman, and a truly remarkable man.

Maurice Pincoffs was elected Editor of the Annals of Internal Medicine at the Annual Session in San Francisco, on April 4, 1932. The first issue of the Annals under his name appeared in January, 1933. Dr. Pincoffs' predecessor was Dr. Aldred Scott Warthin, world-renowned Professor of Pathology at the University of Michigan. His editorship began in 1924 with the Annals of Clinical Medicine, which was renamed the Annals of Internal Medicine in 1927. During the Baltimore meeting of the College he was stricken by illness which proved fatal on May 23, 1931. The duty of carrying on the Annals during the interval between Dr. Warthin's death and Dr. Pincoffs' appointment was assumed by Dr. Carl V. Weller, an associate of Dr. Warthin and his successor to the Chair of

Pathology at Ann Arbor.

Despite all that Dr. Warthin accomplished for the Annals, especially during its most difficult years, the task which faced its new Editor was not easy. At the end of 1932 the Annals, with a circulation of approximately 3,000 copies per month, was little known and comparatively insignificant in the field of internal medicine. Under Dr. Pincoffs' guidance the circulation steadily increased, to the present figure of about 24,000 copies per month. Of even more significance, the Annals today is internationally regarded as the foremost journal in the English-speaking world devoted to internal medicine as it is broadly interpreted. This phenomenal achievement, a tribute to excellent and critical editorial judgment, is due in large part to consistent adherence to the policies which Dr. Pincoffs announced in his initial editorial of January, 1933: "The scope of Internal Medicine should not be defined too narrowly; it blends without sharp boundaries into all the medical sciences and clinical specialties. Nothing in science or practice is truly foreign to its interests." As Editor of the Annals of Internal MEDICINE, Dr. Pincoffs has added immeasurably to the prestige of The American College of Physicians, has stimulated postgraduate medical education, and has created a better understanding of the aims and dignity of internal medicine.

Maurice Pincoffs' contributions to The American College of Physicians are even more far-reaching than his editorial success. Elected as a Fellow

in 1923, he took an active part in the organizational struggles of those early days. Since then, his interest in the College has been unfailing. As a result, he has served the College for 25 years. He served first on the Board of Governors as the College representative for the State of Maryland. Later, he served in various capacities as a Regent until he became President in 1951-52. Since then, by virtue of being Editor of the Annals, Dr. Pincoffs has been an ex officio member of that Board. Each of these groups has depended upon his good judgment and has profited from his statesmanship. Dr. Pincoffs, never arriving at conclusions hastily, proffered his advice only after mature consideration; having thus come to a decision, he held to it without capitulation. On numerous occasions, the wisdom of Dr. Pincoffs' forthright, logical discussions has deterred those governing the College from advocating untimely moves not always in the best interests of our organization. In recognition of his manifold contributions to the College, Dr. Pincoffs was made a Master in 1947, and in 1955 received the coveted Alfred Stengel Memorial Award.

Dr. Pincoffs' admirable personal characteristics and intellectual qualities were noted as early as his undergraduate days at the University of Chicago, while he was a student at The Johns Hopkins University School of Medicine, and during his tours of duty as House Officer. Almost immediately upon completing his formal medical education, young Dr. Pincoffs entered upon his chosen academic career, which has brought him much distinction. His first assignment was as research assistant in pharmacology at the Hopkins; he began his teaching career in clinical medicine as an instructor in medicine at the same institution. In 1922, Dr. Pincoffs was appointed as Head of the Department and Professor of Medicine at the University of Maryland School of Medicine. During his tenure of 33 years in that office, he reorganized the curriculum and in numerous other respects greatly contributed to the advancement and development of that School of Medicine. Not content with becoming emeritus, since 1954 he has enthusiastically engaged in the new career of Professor of Preventive Medicine at the University of Maryland, where he developed a Department of Preventive Medi-This is an activity which has provided him the opportunity to carry on studies in the social and economic problems involved in the rehabilitation of the chronically ill and disabled.

In the course of his long career, Dr. Pincoffs has graced the membership roles of many learned professional organizations, and, in some, he has been the presiding officer. His continuing interest as an investigator is evidenced by over 100 significant contributions to the medical literature. His concern over community health matters has induced him to serve for many years on the Boards of the State and City Health Departments of Maryland and Baltimore. He also became Chairman of a pioneer project, the Committee on Medical Care of the Maryland State Planning Commission.

Dr. Pincoffs is a scholar and brilliant teacher. His students throughout

this and other countries convincingly testify to the high quality of his medical instruction. His early contact with many of the most astute medical minds of the early decades of this century, in conjunction with his large, varied teaching and clinical experience, has been responsible for his critical, precise approach to the difficult problems of medical practice. This has brought him a justly deserved reputation as a diagnostician of unusual acumen and an inspiring preceptor. Students fortunate enough to have been trained by him, appreciating his precepts and example, strive to follow his practice of considering the individual patient as a whole, and exploring diagnostic

problems from every angle.

Dr. Pincoffs' spirit of patriotism, a deeply ingrained trait of his character, found ample opportunity for expression during the two World Wars. Promptly after the United States entered World War I. Dr. Pincoffs, putting aside all other responsibilities, entered the Medical Corps of the United States Army. Throughout that conflict he served as a Captain, first with the British and later with the American troops. His efficient care of those entrusted to his treatment and his "indomitable courage in his personal participation in the evacuation of our wounded from the battlefield" earned him the Distinguished Service Cross and the Croix de Guerre with Palm and Stars (France). Over 22 years later, when this country became engulfed in World War II, Dr. Pincoffs again unhesitatingly offered his services to the nation. He then held the rank of Colonel in the Medical Corps of the Army, and was assigned to highly responsible posts in the Southwest Pacific Theatre, first as Commanding Officer of the 42nd General Hospital, and later as Chief of Preventive Medicine for that area. The excellent morale and effective performance which he inspired among his associates and subordinates were responsible for his being awarded an additional decoration, the Legion of Merit with Oak Leaf Cluster.

Regardless of other obligations, Maurice Pincoffs is primarily a great physician and medical philosopher, who has faithfully followed his guiding dictum, "The essence of Internal Medicine consists in careful clinical observation of disease and its response to treatment." His unselfish devotion to his patients, supplemented by his broad, fundamental knowledge of medical problems, has, in the words of a contemporary colleague, made him a "most respected member of the medical profession of Maryland and one who throughout the United States is regarded as the present-day Oslerian

physician."

As Dr. Pincoffs relinquishes the Editorship of the Annals and is freed from official College responsibilities, let us be ever mindful of his years of wholehearted devotion, loyalty and service to the College. Let us assure him that the Fellowship of the College can never forget his accomplishments, and holds for him great admiration, respect and affection.

GEORGE M. PIERSOL, M.D.

### THE SIGNIFICANCE OF SERUM COMPLEMENT LEVELS FOR THE DIAGNOSIS AND PROG-NOSIS OF ACUTE AND SUBACUTE GLO-MERULONEPHRITIS AND LUPUS ERY-THEMATOSUS DISSEMINATUS\*†

By Kurt Lange, M.D., F.A.C.P., Edward Wasserman, M.D., and Lawrence B. Slobody, M.D., New York, N. Y.

SINCE the original publication by Veil and Buchholz <sup>1</sup> in 1932, in which they reported a lowering of serum complement in a few cases of acute glomerulonephritis, a number of investigators have studied this phenomenon, mostly in small numbers of cases and with short-term observations only.<sup>2, 8, 6</sup>

For the last 10 years 5, 6 we have examined serum complement levels in 3,051 patients with varied kidney diseases, in addition to examinations in a great number of normal persons, and in patients with other disease conditions. Since we felt that the determination of serum complement levels (C') is an important and often decisive aid in the diagnosis and prognosis of renal diseases, a method had to be devised which was simple enough to be carried out in a routine serologic laboratory but so accurate as to preclude misleading information.

Table 1 shows the method used. The sera were examined within 24 hours after they were drawn, or were frozen at minus 35° C. until they were studied. They were serially diluted with a barbiturate buffer of pH 8.6 containing magnesium. Two tenths of a milliliter of buffer, and thereafter 0.2 ml. of sensitized sheep cells, were added. The sheep cells were sensitized with three units of anti-sheep-cell hemolysin. The row of tubes is then incubated in a water-bath for one hour at 37° C. with repeated shaking, and then kept in the refrigerator at 5° C. overnight to permit settling of the unlysed cells. The next day it is read for the 50% hemolysis end point. The values read were related to the 50% hemolysis value obtained from a test row, using standard guinea pig complement. The hemolysis induced by a 1:8 dilution of standard guinea pig complement was called one unit, and the values obtained from the human sera also read for 50% hemolysis were related to this standard value. In our experience, the omission of the

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use of such a standard in each test introduces a considerable error and should be discouraged.

When 103 selected normals were examined, the C' values varied between 1.2 and 4.0 units, with an average of 2.4 units and a standard deviation of 0.62.

Altogether, the sera of 291 cases of acute glomerulonephritis were studied. Some of the sera were sent to us from other institutions. Since we did not have a chance to follow these outside cases clinically, they were omitted from our statistics, leaving us with a total of 246 patients, of whom 171 (69%) were children and 75 were adults. All fulfilled the criteria of

Table 1
Technic of Complement Determination
(°/H50)

Serum 0.2 ml. dilutions with barbiturate buffer + Mg	Undi- luted	1:2	1:4	1:8	1:16	1:32	1:64	1:128
Barbiturate buffer + Mg ml.:	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
2.5% Sheep cell susp. sensitized with 3 units of hemolysin ml.:	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Incubated in water bath for 60 min. at 37° C.

24 hrs. in refrigerator at +5° C. Reading for 50% hemolysis.

Correction according to the value for the standard guinea pig C'.

an antecedent sore throat or febrile upper respiratory infection, many had frankly bloody urines, all except one had microscopic hematuria, and 62% had red cell casts. Antistreptolysin O titers were elevated in 85% of those where they were examined. The initial complement value, as shown in figure 1, was low in all cases except one. The average of the initial values in this group with acute glomerulonephritis was 0.49 unit, or about one fifth of the average of the normals. The standard deviation was 0.322. One adult had a low normal C' value, but in spite of this normal value we had every reason to assume from the clinical data that we were dealing with an acute glomerulonephritis. A kidney biopsy could not be done. The patient recovered completely within two weeks.

In contrast to acute glomerulonephritis, C' is at least normal or more often high in acute and also in chronic pyelonephritis.

Serum complement levels in glomerulonephritis behaved in three different ways after the initial lowering.

In the first group, representing by far the majority of cases, C' levels remained low for several weeks; then they returned to normal, coincidentally with a gradual clearing of the disease. Those patients who had a moderate initial lowering of C' usually showed a disappearance of all signs and symp-

toms, including abnormal Addis counts, shortly before the return of C' to normal. Those who had a marked initial lowering of C', sometimes to zero, always had a more prolonged and stormy course, as typified by the case shown in figure 2. The C' values here rose very slowly; the clinical findings, especially blood pressure and nitrogen retention, remained high for prolonged periods of time. When complement finally returned to normal, there was a period of several days when the Addis count was still elevated. This may be explained by the fact that the prolonged closure of many glomeruli by

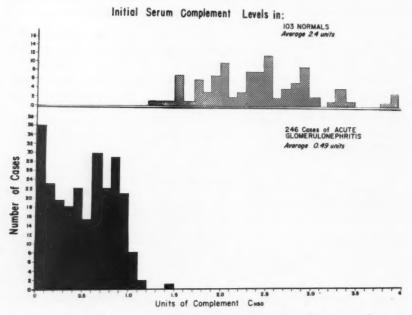


Fig. 1. Initial serum complement levels in 103 normals and 246 cases of acute glomerulonephritis.

endothelial swelling may have led to severe capillary damage, with subsequent rhexis, lasting beyond the time of subsidence of the basic immunologic process. The end result, however, is complete healing without residue.

The second group was represented by 10 cases, all having initial C' values below 0.28 unit, and no marked rise or return to normal until death. All 10 patients died in uremia within four years; the average survival from the onset of disease to death was 2.8 years. It thus appears that the persistence of low C' levels indicates a very poor prognosis, with continuation of the basic immunologic disease and a rapid decline of kidney function.

The third group was composed of cases suffering from what is commonly

called chronic glomerulonephritis, where C' was normal but signs of marked kidney damage existed. These cases seemed to have a much better prognosis than the second group, although diminishing clearance values in some seemed to indicate a poor *long* range prognosis. It remains to be seen whether they actually are healed cases, with increasing reduction of kidney function due to shrinkage and fibrosis, or whether the immunologic activity

# Serum Complement and Clinical Course in a Case of Acute Glomerulonephritis

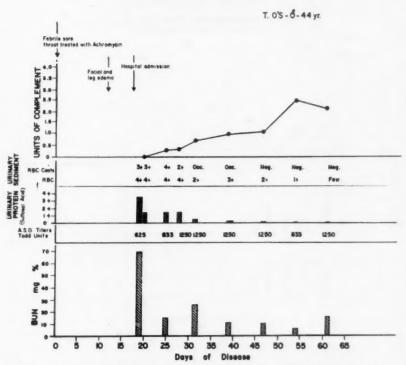


Fig. 2. Serum complement and clinical course in a case of acute glomerulonephritis with slow healing.

is of such a low degree that the over-all C' level is not depressed, since only a small number of glomeruli are involved in the active process. One can also consider the possibility that in some cases with a marked reduction of active glomerular surface, especially those in uremia, the antigenic area has become too small to lead to a fall in C'.

This point can be illustrated by certain animal experiments. In rabbits from which we removed surgically about 65% of their kidneys, the injection

of nephrotoxic serum led only to a very slight fall in C', but to a severe disease with rapid death in uremia. In contrast, the control animals with normal kidneys, receiving the same amount of nephrotoxic serum, showed a very marked fall in C' with moderately severe glomerulonephritis.

Figure 3 shows the pertinent data of a patient with a stormy initial course, with very low C' levels, who improved slowly but remained with a tendency to marked hematurias whenever she had a fresh upper respiratory infection, not necessarily streptococcal in origin. This case may be appropriately called "subacute glomerulonephritis."

## Serum Complement and Clinical Course in a Case of Acute Glomerulonephritis

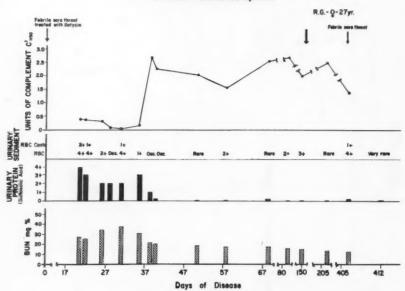


Fig. 3. Serum complement and clinical course in a case of acute glomerulonephritis continuing with a subacute phase.

On the other hand, certain hematurias may masquerade as acute glomerulonephritis, and it is only by C' determinations that the real diagnosis can be made. We received 13 sera from an epidemic outbreak of acute glomerulonephritis in an Army camp. All 13 patients had hematuria. Twelve sera had varying degrees of lowering of C', while one serum on repeated examinations showed normal values. This patient was reëxamined and a bleeding polyp of the bladder was found.

To illustrate further the importance of C' determinations, the following cases are mentioned. A five year old girl was admitted to our wards for hematuria one week after she had had a severe sore throat. The diagnosis

of acute glomerulonephritis was made on the basis of the history, of frank hematuria, general malaise, and an antistreptolysin O titer of 833 Todd units. C', however, was repeatedly normal. The reëxamination of the abdomen of the patient revealed a moderate enlargement of the left kidney which, on operation, turned out to be a Wilms's tumor, with invasion of the vasculature.

Conversely, a 36 year old male was admitted for cardiac failure, with all signs of right heart failure. The blood pressure was elevated to 170/90 mm. Hg, and a moderate number of red cells were found in the urine. The patient was treated as being in cardiac failure, without the expected effect.

## Initial Serum Complement Levels in:

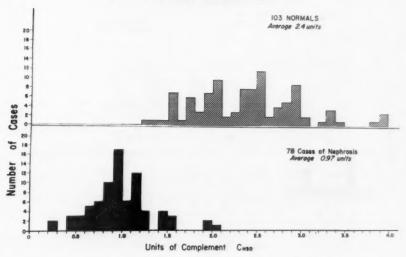


Fig. 4. Initial serum complement levels in 103 normals and 78 cases of nephrosis.

C' determination revealed a value of 0. A kidney biopsy done thereafter showed markedly hypercellular swollen glomeruli, with an increase in polymorphonuclear neutrophils. After a prolonged and stormy course, the patient recovered completely.

We have studied the C' levels in 75 cases of pure nephrosis. Figure 4 shows the initial values found in these cases. In general, the lowering of C' in nephrosis is not nearly as severe as in acute glomerulonephritis, and 15% of the cases showed normal C' values. Loss of C' into the urine cannot be used as an explanation of this depression, since, besides other evidence, C' is not lowered in the diabetic nephrotic syndrome, in renal amyloidosis, or in myeloma kidneys with equally massive proteinurias.

The number of cases where kidney biopsy results could be compared with the C' level is still too small. So far it appears that C' is depressed when such signs of acute glomerular inflammation as hypercellularity and polymorphonuclear invasion are present, but is normal when these features are absent.

Since the initial publication by Vaughan <sup>7</sup> and collaborators in 1951, a number of investigators have confirmed their finding of a marked lowering of C' in active cases of lupus erythematosus disseminatus.<sup>8, 9</sup> We have studied 43 cases (figure 5). Eleven of these (25%) had anticomplementary sera and were excluded from our statistics. This well known high incidence of anticomplementary sera among patients with systemic lupus, however, can help in a given case to confirm the clinical impression of the

## Initial Serum Complement Levels in:

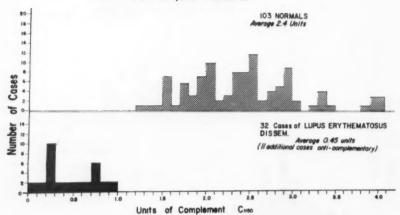


Fig. 5. Initial serum complement levels in 103 normals and 32 cases of lupus crythematosus disseminatus.

presence of the disease. The C' values found in the remaining 32 cases were all markedly subnormal as long as clinical activity persisted; the average was 0.45 unit, or approximately one fifth of normal. Recently, Ellis and Felix-Davies <sup>8</sup> reported that, even in most cases with anticomplementary sera, using a special technic to study such lupus sera, C' is actually low. Four of our lupus cases with low C' had no evidence of renal involvement, and one had a normal kidney biopsy. Three cases had three negative lupus cell preparations at the time C' was found to be low. In two the lupus preparation subsequently became positive.

With steroid treatment, C' slowly becomes normal, although lupus cell preparations often become negative and clinical signs disappear before the return of C' to normal. Figure 6 shows the course in a nine year old girl with systemic lupus of moderate degree. The initial C' value was 0.71 unit. The patient was treated with a 30-day course of 80 mg. of prednisone per day, followed by a prolonged intermittent regimen of triamcinolone, 48 mg.

per day initially for four and later for three successive days of each week. This resulted in a return of C' to normal, in this case several months before the lupus cell preparations became negative. While we are at present trying this type of treatment, which we originally suggested for the treatment of nephrosis, we are not recommending it as yet, since not enough is yet known about its efficacy. The rebound phenomenon as seen in this case, with a

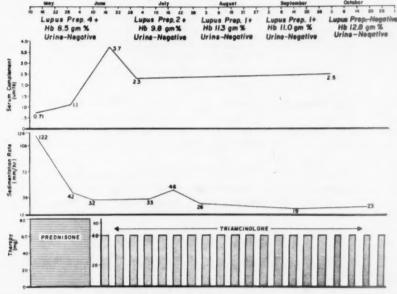


Fig. 6. Complement, sedimentation rate and lupus preparations in a patient with lupus erythematosus disseminatus under treatment with prolonged intermittent steroid therapy.

value of 3.7 units, is a common occurrence with the clearing of disease in glomerulonephritis as well as in lupus. In lupus and in nephrosis, it is a good prognostic sign. Since the lupus phenomenon can occasionally be found in rheumatoid arthritis, in which C' is either normal or high, the determination of C' can well serve to differentiate the two diagnoses. Holman <sup>10</sup> and others have doubted that the antibody against desoxyribonucleic acid, histone and related substances found in the sera of patients with systemic lupus, and manifested in the lupus cell phenomenon, has any relation to the basic mechanism of this disease. The persistent finding of low C' values in these patients tends to strengthen the idea, however, that an antigenantibody reaction may play an important role in this disease, not only in vitro but also in vivo.

Since only a few other rather rare conditions lead to a lowering of serum C' (table 2), the determination of the C' level may serve as an important guide in the differential diagnosis of renal diseases.

There can be four reasons why C' is low:

1. Excessive loss of C' (e.g., into the urine) could lead to a lowering. This can be excluded in glomerulonephritis, where the lowest values are usually found during the anuric or markedly oliguric phase, and the proteinuria in general is mild. In lupus, low values are found even in the absence of renal damage. In the nephrotic syndrome, low C' values are found only in the pure nephrosis, and not in other nephrotic syndromes with proteinurias of equal or higher degree.

TABLE 2

The Use of Serum Complement Levels in the Differential Diagnosis of Renal Diseases

Serum Complement was Normal or High in:

Wilms's tumor Sulfa-hematuria Ureteral calculus T.B. kidney Pyelonephritis Kimmelstiel-Wilson's disease Amyloidosis of the kidney Toxemia of pregnancy Rheumatic fever Febrile diseases including tonsillitis

Serum Complement was Low in:

The edematous phase of serum sickness The edematous phase of trichinosis Acute glomerulonephritis Nephrosis Active lupus erythematosus disseminatus

2. C' can be lowered by interaction with anticomplementary substances. This could be excluded in all cases of systemic lupus described here, and in all but one case of acute glomerulonephritis not used in the statistics.

3. C' can be low by decreased production. This possibility is not completely excluded, since we know very little about the formation of complement. In experimental nephritis, however, one can show that complement levels remain normal if the kidneys are removed shortly before the expected onset of clinical renal disease. This suggests that there may be normal production with fixation in the diseased kidneys. In addition, even severe disproteinurias in advanced liver diseases do not lead to a lowering of C'.

4. C' can become lowered by increased utilization in antigen-antibody reactions. Indeed, Seltzer et al. and Rice have shown that an animal can be partially or completely decomplemented by injecting antigen-antibody complexes. We could show that, in the perfusion of isolated rat kidneys, complement is removed from the perfusing serum by the kidney when nephrotoxic serum is added. Finally, Klein and Burkholder recently confirmed this finding by the use of a fluorescein-labeled antibody against complement. They showed that complement is indeed fixed on the basement membrane of the glomeruli in experimental glomerulonephritis.

As a result, it appears highly probable that the reduction of C' in glomerulonephritis and systemic lupus is due to this increased utilization in an antigen-antibody reaction. Thus the finding of lowered complement in these diseases not only appears to be a valuable diagnostic and prognostic tool, but also seems to give us some insight into the basic mechanism of the conditions.

#### SUMMARY

1. Serum complement levels were markedly lowered in 245 out of 246 cases of acute glomerulonephritis. Complement returned to normal in most cases at approximately the time when healing occurred. Other hematurias were not accompanied by low complement levels.

2. Persistence of low complement levels seems to indicate a very poor

prognosis, with rapid decline of kidney function and death.

3. In chronic glomerulonephritis, serum complement values were normal.

4. In 75 cases of pure nephrosis, complement levels were lowered in 85% of the cases. Complement levels were normal in other nephrotic syndromes, e.g., the diabetic nephrotic syndrome, in patients with renal amyloidosis and myeloma kidneys.

5. Anticomplementary sera were found in 25% of 43 cases of active lupus erythematosus disseminatus. The remaining 32 cases all showed markedly lowered serum complement levels, whether or not there was any

kidney involvement.

6. The possible reasons for the lowering of serum complement levels are discussed. The fall must be assumed to be due to a binding of complement in an antigen-antibody reaction.

#### SUMMARIO IN INTERLINGUA

Le nivellos seral de complemento esseva studiate in 3.051 patientes con varie nephropathias. Esseva elaborate un methodo satis simple pro usos routinari in le laboratorio serologic sed satis accurate pro garantir le exclusion de informationes erronee. Le studio de un specimen standard de complemento de porco de India in omne batteria de specimens a testar es apparentemente de importantia special pro le obtention de resultatos accurate.

In un gruppo de 246 patientes con le diagnose clinic de acute glomerulonephritis—69% juveniles e 31% adultos—omnes, con un exception, habeva marcatemente reducite nivellos seral de complemento. Le complemento retorna a nivellos normal con le curation clinic del morbo. Per contrasto con isto, in pyelonephritis acute o chronic le valores pro le complemento es normal o elevate. Dece patientes con acute glomerulonephritis e permanentemente bassissime valores de complemento habeva prognoses non bon del toto. Omnes moriva intra quatro annos in uremia, con un superviventia medie de 2,8 annos. In glomerulonephritis chronic, le nivello del complemento es normal.

Hematurias de origine obscur pote esser differentiate ab glomerulonephritis per tests del complemento, e—inversemente—iste tests servi a vices a provar que un patiente con disfallimento cardiac a origine obscur suffre de facto de acute glomerulonephritis. In circa 75% del casos de un serie de 75 patientes con nephrosis pur,

le nivello del complemento seral esseva basse. Isto non resultava de un perdita de complemento via le excretion urinari o del action de substantias anti complemento.

In le micre numero de casos in que biopsias renal esseva effectuate simultaneemente con le determinationes de complemento, hypercellularitate glomerular e invasion polymorphonucleari del glomerulos pareva occurrer in parallela con le reduction del complemento.

Inter 43 casos de disseminate lupus erythematose, 11 monstrava sero anticomplementari. In le alteres, le nivellos del complemento esseva marcatemente reducite, sin reguardo a si o non le renes esseva demonstrabilemente implicate. Sub therapia steroidic, le nivellos del complemento retornava al norma, precisemente como in casos de nephrosis.

Es discutite le rationes pro le reduction del complemento in iste varie conditiones. Le phenomeno es ascribite, con alte grados de probabilitate, a reactiones de antigeno e anticorpore in que le complemento es ligate. Determinationes de complemento es un methodologia importante e frequentemente decisive in le diagnose differential del morbos renal.

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## LIMITS TO FUNCTIONAL HYPERTROPHY IN HIGH-OUTPUT FAILURE \*

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#### INTRODUCTION

HIGH-OUTPUT failure in man has been described both for cardiac blood propulsion 1 and for bone marrow erythropoiesis, 2 but it also occurs in a wide variety of processes in other organs. It seems implicit in all descriptions of "relative failure" or "relative insufficiency" of the function of an organ.<sup>2</sup> The usual response of an organ process when it remains subjected to increased loads is a secondary increase in the capacity to perform the affected function. Such functional hypertrophy has limits, beyond which the increased capacity becomes inadequate for the increasing load. At this point, failure of the function becomes evident despite output levels greater than normal. There appear to be both normal and pathologic limits to an increase in capacity for a given function. This article will review from the literature various examples of high-output failure in man, and will illustrate the occurrence of pathologic limits to the increase of capacity in certain of these examples.

#### HISTORY

Meltzer in 1906 first discussed the reserve capacity of many different body processes in man, with emphasis on the ability of organs to reach performance levels above those occurring normally.3 With the subsequent intensive development of quantitative technics in human physiology, increased activity of organ processes could be detected in diverse disease states. By 1925, Liljestrand and Stenstrom could demonstrate high-output cardiac failure in patients with thyrotoxicosis or severe anemia.4 In 1940 Dameshek and Schwartz could summarize evidence for high-output marrow erythropoietic failure in patients with acute hemolytic anemia.<sup>5</sup> Huckabee, Caston and Harrison, in 1950 classified cardiac failure types by physiologic categories, including an increased-load, high-output failure state.<sup>6</sup> In 1952 Crosby and Akeroyd first determined both the normal and the pathologic limits to maximal hypertrophy of marrow erythropoiesis, and Singer in 1955 termed the submaximal pathologic state "dyserythropoiesis." 8 By 1957 Moore was able to describe examples of selective high-output failure of each of the three basic bone marrow functions,2 and recently the hypo-

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albuminemia of patients with the nephrotic syndrome has been ascribed to high-output failure of hepatic albumin synthesis.<sup>9</sup>

#### DOCUMENTED EXAMPLES

The following body processes have been well shown to display highoutput failure in certain disease states, with each of these also demonstrating pathologic limits to maximal hypertrophy of capacity (table 1).

Table 1
Well Documented Examples of High-Output Failure (see text)

Organ	Function	Hypertrophy to Normal Limit Disease State	Maximal Increase (% normal)	Hypertrophy to Patho- logic Limit Disease State	Maximal Increase (% normal)
Bone marrow	Hemoglobin synthesis	Congenital sphero- cytosis	600-800	Sickle cell anemia	200-400
Heart	Blood propulsion	Thyrotoxicosis	300	Athiaminosis	200
Liver	Albumin synthesis	Plasma donor	400	Nephrotic syndrome	200
Bone osteoid	Osteoid calcification	Paget's disease (ostei- tis deformans)	500	Thyrotoxic osteoporo-	150
Pulmonary vasculature	Blood flow conduction	Childhood atrial septal defect	400-600	Adult atrial septal defect	300
Kidney	Ammonium synthesis	Early diabetic acidosis	500	Azotemic diabetic acidosis	300
Thyroid	Iodide organification	Congenital goitrous cretin	1,000	Nephrotic syndrome	150
Liver	Aldosterone inactiva-	Normal pregnancy	700	Toxemic pregnancy	400
Pancreatic islets	Insulin synthesis	Fetus of prediabetic mother	3,600	Growth acromegaly	2,000

1. Hemoglobin Synthesis: In normal subjects the rate of hemoglobin synthesis is 6.25 gm./70 Kg./day.<sup>7,10</sup> In patients with congenital spherocytosis this rate is often maximally increased to 600 to 800% of normal,<sup>7,10,11</sup> but, by contrast, in patients with sickle cell anemia this rate is not increased to more than 200 to 400% of normal, despite continued anemia.<sup>7,10,11</sup> This appears to indicate a pathologic limit to full hypertrophy of bone marrow capacity to synthesize hemoglobin in patients with sickle cell anemia, and it may be related to the extensive fibrotic lesions in the bone marrows of these patients.<sup>12</sup>

Despite these increased rates, high-output failure of bone marrow hemoglobin synthesis in both of these diseases is evidenced by the anemia (whole blood hemoglobin < 12 gm.%) that these patients display. Pathologic limits to full hypertrophy of bone marrow capacity to synthesize hemoglobin are similarly present in patients with the high-output failure states of pernicious anemia, 11, 13 acquired immunohemolytic anemia, 16, 11 thalassemia major, 11, 14 hepatic cirrhosis, 11, 15 chronic lymphatic leukemia, 16 myeloid metaplasia and disseminated carcinoma. 17

2. Blood Propulsion: In normal resting subjects the rate of cardiac output is 3.0 to 3.5 L./min./M<sup>2</sup>. In patients with thyrotoxicosis this rate is often maximally increased during rest to 300% of normal, but, by contrast, in patients with athiaminosis this rate is not increased during rest to

more than 200% of normal,<sup>20</sup> despite continued congestive failure. This appears to indicate a pathologic limit to full hypertrophy of cardiac capacity to propel blood in patients with athiaminosis, and it may be related to the deleterious effects of athiaminosis on oxidative phosphorylation in cardiac muscle.<sup>21</sup>

Despite these increased rates, high-output failure of cardiac propulsion of blood in both of these diseases is apparent in the hemodynamic evidence of congestive failure (ventricular end-diastolic pressure > 10 mm. Hg) that these patients display.<sup>19, 20</sup> Pathologic limits to full hypertrophy of cardiac output are similarly present in patients with the high-output failure states of severe chronic anemia <sup>22</sup> and chronic cor pulmonale.<sup>23</sup>

3. Albumin Synthesis: In normal subjects the rate of albumin synthesis is 13.0 gm./70 Kg./day.<sup>24</sup> In normal plasma donors in whom the erythrocytes are re-infused after separation from the plasma this rate is often maximally increased to 400% of normal,<sup>25</sup> but, by contrast, in patients with the nephrotic syndrome in relapse this rate is not increased to more than 200% of normal,<sup>26</sup> despite continued hypoalbuminemia. This appears to indicate a pathologic limit to full hypertrophy of hepatic capacity to synthesize albumin in patients with the nephrotic syndrome in relapse, and it may be related to hepatic hypometabolism secondary to the excessive urinary loss of thyroid hormone seen in these patients.<sup>27</sup>

Despite these increased rates, high-output failure of hepatic albumin synthesis in both of these states is evidenced by the hypoalbuminemia (plasma albumin < 2.5 gm.%) that these patients display.

4. Osteoid Calcification: In normal subjects the rate of osseous calcification of bone osteoid is 0.08 to 0.17 distal calcium pools/70 Kg./day.<sup>28</sup> In patients with extensive Paget's disease (osteitis deformans), this rate is often maximally increased to 500% of normal,<sup>28</sup> but, by contrast, in patients with severe thyrotoxic osteoporosis this rate is not increased to more than 150% of normal,<sup>28</sup> despite continued microscopic evidence of uncalcified osteoid. This appears to indicate a pathologic limit to full hypertrophy of the osseous capacity to calcify bone osteoid in patients with severe thyrotoxic osteoporosis, and it may be related to increased osseous blood flow in these patients.<sup>28</sup>

Despite these increased rates, high-output failure of osseous calcification of bone osteoid is evidenced in both diseases by the uncalcified bone osteoid seen microscopically in these patients.<sup>29</sup>

5. Pulmonary Vascular Flow: In normal resting subjects the rate of pulmonary vascular flow is 3.0 to 3.5 L./min./M<sup>2.18</sup> In children with atrial septal defect this rate is often maximally increased during rest to 400 to 600% of normal, <sup>30</sup> but, by contrast, in adults with atrial septal defect this rate is not increased during rest to more than 300% of normal, despite continued pulmonary hypertension. <sup>30</sup> This appears to indicate a pathologic limit to full hypertrophy of the pulmonary vascular capacity to conduct

blood in adult patients with atrial septal defect, and it may be related to the proliferative pulmonary endarteritis seen in these adult patients.<sup>31</sup>

Despite these increased rates, high-output failure of pulmonary vascular conduction of blood in both of these states is evidenced by the pulmonary hypertension (pulmonary artery systolic pressure > 30 mm. Hg) that these

patients display.80

6. Ammonium Production: In normal subjects the rate of renal ammonium production is 30 to 50 mEq./70 Kg./day.<sup>32</sup> In patients with diabetic acidosis but without azotemia this rate is often maximally increased to 500% of normal,<sup>33</sup> but, by contrast, in patients with diabetic acidosis in whom azotemia has supervened this rate is not increased to more than 300% of normal,<sup>34</sup> despite continued evidence of plasma acidosis. This appears to indicate a pathologic limit to full hypertrophy of the renal capacity to produce ammonium ion in patients with diabetic acidosis in whom azotemia has supervened, and it may be related to the deleterious effect of decreased renal blood flow on tubular function in these patients.<sup>85</sup>

Despite these increased rates, high-output failure of renal production of ammonium ion in both of these states is evidenced by the plasma acidosis

(plasma pH < 7.35) that these patients display.<sup>36</sup>

7. Iodide Organification: In normal subjects the rate of thyroidal iodide organifications is 50 to 150  $\mu$ g./70 Kg./day.<sup>37</sup> In patients with congenital goitrous cretinism this rate is often maximally increased to 1,000% of normal,<sup>38</sup> but, by contrast, in patients with the nephrotic syndrome in relapse this rate is not increased to more than 150% of normal,<sup>39</sup> despite continued hypometabolism and subnormal plasma organic iodine levels. This appears to indicate a pathologic limit to full hypertrophy of the thyroidal capacity to organify iodide in patients with the nephrotic syndrome in relapse, and it may be related to the deleterious effect of general body protein depletion on pituitary production of thyrotropin in these patients.<sup>39</sup>

Despite these increased rates, high-output failure of thyroidal organification of iodide is evidenced in both diseases by the hypometabolism and deficiency of thyroid hormone (serum protein-bound iodine  $< 3.0 \mu g.\%$ )

that these patients display.38, 89

8. Aldosterone Inactivation: In normal subjects the rate of hepatic inactivation and conjugation of aldosterone is 3.0 µg./70 Kg./day.<sup>40</sup> In patients during normal pregnancy this rate is often maximally increased to 700% of normal,<sup>41</sup> but, by contrast, in patients during toxemic pregnancy this rate is not increased to more than 400% of normal,<sup>41</sup> despite the continued presence of increased quantities of active "free" aldosterone. This appears to indicate a pathologic limit to full hypertrophy of the hepatic capacity to inactivate and conjugate aldosterone in patients during toxemic pregnancy, and it may be related to the thrombonecrotic lesions in the livers of these patients.<sup>42</sup>

Despite these increased rates, high-output failure of hepatic inactivation

and conjugation of aldosterone is evidenced in both states by the elevated levels of active "free" aldosterone in the urine (urine "free" aldosterone  $> 1.0 \,\mu g./70 \,\mathrm{Kg./day}$ ) that these patients display.<sup>41</sup>

9. Insulin Synthesis: In normal subjects the rate of pancreatic islet synthesis of insulin is 48 units/70 Kg./day.<sup>43</sup> In the fetuses of prediabetic mothers this rate is often maximally increased to 3,600% of normal,<sup>44</sup> but, by contrast, in adult patients with "growth" acromegaly this rate is not increased to more than 2,000% of normal,<sup>45</sup> despite continued evidence of insulin deficiency and intolerance for glucose. This appears to indicate a pathologic limit to full hypertrophy of the pancreatic islet capacity to synthesize insulin in patients with "growth" acromegaly, and it may be related to the proliferative islet lesions produced by growth hormone.<sup>46</sup>

Despite these increased rates, high-output failure of pancreatic islet synthesis of insulin is evidenced in both states by the insulin insufficiency (increased weight and stillbirth rate in fetuses,<sup>47</sup> glucose intolerance in adults <sup>48</sup>) that these patients display.

## SUGGESTIVE EXAMPLES

Additional suggestive examples in man of high-output failure and of the normal and pathologic limits to increased capacity are outlined in table 2.

TABLE 2
Suggestive Examples of High-Output Failure

Organ	Function	Hypertrophy to Normal Limit Disease State	Reference	Hypertrophy to Patho- logic Limit Disease State	Refer
Bone marrow	Granulocyte production	Endotoxin leukopenia	49	Immuno-agranulo- cytosis	80, 51
Sweat glands	Sweat secretion	Thyrotoxic storm	80	Thermogenic anhidrosis	50, 54
Liver	Fibrinogen synthesis	Fibrinolytic purpura	58	Abruptio placentae	86
Kidney	Uric acid excretion	Early leukemia	57, 58	Azotemic leukemia	20
Liver	Triglyceride catabolism	Diabetic ketosis	60, 61, 62	Diabetic acidosis	58.
Bone marrow	Platelet production	Idiopathic thrombo- cytopenic purpura	63, 64	Immunothrombo- cytopenia	64
Parathyroid	Parathormone produc-	Vitamin D deficiency	45	Chronic uremia	66

Physiologic technics for quantitating function in these organ processes in man have not yet been applied or are still too imprecise to permit definitive documentation.

## Discussion

It seems apparent that an organ can fail in performing a given function in either an "absolute" or a "relative" manner. "Absolute failure" of a body process implies inadequate output when the process is presented with normal loads of work to be accomplished. "Relative failure" implies supernormal but nevertheless inadequate output when the process is presented with greater-than-normal loads.

Of fundamental interest is the ability of an organ to increase its capacity when subjected to prolonged increases of imposed loads. Acutely increased loads to an organ usually lead to a state of temporary disequilibrium, which tends to be moderated by the body mechanisms for homeostasis, <sup>67</sup> resulting either in the rapid, increased utilization of previously unused reserve capacity in the organ, or in the slow, new formation of increased capacity. Homeostatic mechanisms which increase capacity can operate entirely within the affected organ, as in the sensitivity of the liver cells to hypoalbuminemia, <sup>68</sup> or in the responsiveness of cardiac muscle to increased stretching; <sup>69</sup> or they can operate by increased activity of a second organ, as in the increased production of erythropoietin by the anemic kidney, <sup>70</sup> or in the increased production of corticotropin by the hypocorticoid pituitary. <sup>71, 72</sup>

Functional hypertrophy in a given process can thus be pathologically limited either by an inadequate stimulation from the homeostatic mechanism or, as seems more frequent, by the inability of the failing organ to respond to such homeostatic stimulation. Such inability often seems to be a direct consequence of the disease process, as in the bone marrow fibrosis in patients with sickle cell anemia, 12 in the pulmonary endarteritis in adults with atrial septal defect, 31 or in the thrombonecrotic hepatic lesions in patients with toxemic pregnancy. 42

Such limiting lesions may be much more difficult to treat than are the abnormally large loads imposed on the failing organ. Reduction of such loads is the essence of successful therapy in disease states of high-output failure.

#### SUMMARY

The widespread occurrence of high-output failure in man has been reviewed for both well documented and suggestive examples.

The occurrence of pathologic limits to functional hypertrophy in each of these processes has been illustrated.

The failure of homeostasis implicit in such pathologic limits has been discussed.

#### SUMMARIO IN INTERLINGUA

Un revista del litteratura clinic revela numerose exemplos, in subjectos human, de disfallimento a elevate nivellos de performance del parte de processos corporee in un extense varietate de organos e de statos pathologic. Certe exemplos es citate in le quales datos quantitative es disponibile. Il es un phenomeno usual que un processo particular in le organismo augmenta su capacitate pro executar su function in le presentia de un augmentate carga. Sed tal augmentos de capacitate ha lor limites tanto normal como etiam pathologic. Quando le limite del augmento del capacitate as excedite per le carga, disfallimento del function corporee in question es evidente in despecto de nivellos de performance in supra del norma. Iste genere de disfallimento se explica (1) per le inadequatia del stimulo que deberea inducer le processo a augmentar su intensitate o (2) per le incapacitate del processo de responder al stimulo. Il pare que certes del pathologic factores limitatori pote esser attaccate per

mesuras therapeutic, sed le essentia del successose therapia in statos de disfallimento a alte performance es le reduction del augmentate carga imponite super le disfallente organo.

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## ACUTE LEUKEMIA AND PREGNANCY\*

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THE reported instances of concurrent acute leukemia and pregnancy number approximately 100. By and large, this number is made up of isolated case reports and cases culled from reviews of the literature. 1-8 The largest single series of cases of acute leukemia previously reported consists of four.7,9 Most reports group both the acute and the chronic leukemias together (the latter group consisting of the greater number of cases), and, as most authors have pointed out, the experience at any one center is extremely limited. From this, one might infer that the management of such patients is only infrequently a matter of clinical concern. However, during the last five years we have encountered eight pregnant women with acute leukemia. With the rising incidence of acute leukemia, and the potentiality of prolonging life with the antileukemic agents, the problem can be expected to assume increasing importance. The following cases are reported to emphasize the incidence and complexity of the problem, and to offer a rationale for management.

#### CASE REPORTS

Case 1 (figure 1). This 29 year old white woman had been essentially well until early December, 1953, at which time she noted the sudden onset of an upper respiratory infection, with high fever, frontal headaches and weakness. She was treated with penicillin for approximately 10 days, with subsidence of the acute symptoms, although the weakness persisted. In January, 1954, a molar tooth was extracted, with severe bleeding and incomplete healing. The patient returned to her family physician, who made a diagnosis of anemia and treated her with vitamin B<sub>19</sub> and antibiotics. During the next two weeks her symptoms progressed rapidly, with marked weakness, severe ease of fatigue, daily fever and night sweats. She was hospitalized elsewhere, a diagnosis of leukemia was made, and she was treated with multiple transfusions (13 units), antibiotics and a course of irradiation to the spleen. This was followed by several days of cortisone. In March, 1954, because of the continued need for transfusions, she was transferred to the Simpson Memorial Institute.

Physical examination on admission revealed an acutely and chronically ill white female, with marked dorsal kyphosis, a temperature of 102° F., a pulse of 130, and a weight of 88 pounds. Superficial oral ulcerations were prominent over the palate,

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with hyperemia of the pharynx and ulceration over a hypertrophied left tonsil. The anterior cervical lymph nodes were enlarged and tender, and sternal tenderness was present. Severe kyphoscoliosis made measurement difficult, but the liver was palpable 13 cm. below the right costal margin and the spleen 4 cm. below the left costal margin.

Laboratory examination revealed: hemoglobin, 8.5 gm. (54%); red blood cells, 2.7 × 10<sup>6</sup>/mm.<sup>3</sup>; hematocrit, 25 vol.%; white blood cells, 850/mm.<sup>3</sup>, with a differential of polymorphonuclears, 5%; large lymphocytes, 59%; small lymphocytes, 29%; monocytes, 4%; eosinophils, 1%; blast cells, 2%. The platelets were moderately decreased. The antibody studies were all within normal limits. Bone marrow

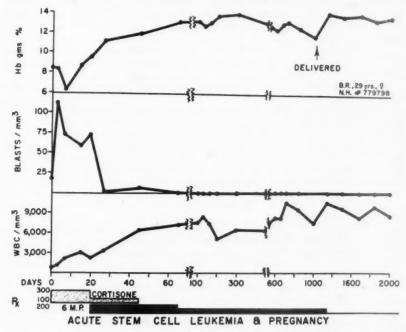


Fig. 1. Case 1. Acute stem cell leukemia antedating pregnancy by two and one-half years. Conception occurred while patient was on 50 mg. of 6-mercaptopurine per day. Patient is presently in complete remission.

aspiration revealed that almost 100% of the cells were primitive, undifferentiated hemocytoblasts. A diagnosis of acute stem cell leukemia was made.

The patient's early hospital course was stormy, with temperature spikes to 105° F. Penicillin, streptomycin and 300 mg. of cortisone per day were given. During the next two weeks the patient's toxicity slowly subsided. The cortisone was then slowly tapered, and 6-mercaptopurine, 100 mg. per day, was instituted. Her status slowly improved, and she was discharged to her home on 50 mg. of 6-mercaptopurine per day in May, 1954. At the time of discharge her hemoglobin was 11.5 gm. (73%); red blood cells, 3.6 × 10<sup>6</sup>/mm.<sup>3</sup>; hematocrit, 36 vol.%; white blood cells, 3,600/mm.<sup>3</sup>, with polymorphonuclears, 63%; large lymphocytes, 11%; small lymphocytes, 11%; monocytes, 11%; blasts, 3%. Platelets were present in normal

numbers. A bone marrow at this time showed marked improvement, with active normoblastic erythropoiesis and maturation of the granulocytic series to the point that

all forms were represented, although 25% of the cells were stem cells.

The patient was followed serially in the outpatient clinic, with blasts noted in the peripheral blood during the next several weeks. A repeat bone marrow late in June, 1954, revealed an erythrocyte: granulocyte ratio of 1:1, with notable atypicality of the granulocytic series and an increased number of monocytoid progranulocytes and myelocytes.

In October, 1956, while still on 50 mg. of 6-mercaptopurine per day, the patient became pregnant. The pregnancy was not recognized until the fourth month of gestation. The 6-mercaptopurine was then withheld for eight days, after which the decision was reached to re-institute therapy, because after thorough obstetric evaluation it was felt that the patient had already passed through the crucial first trimester of gestation.

A normal, healthy, term, six and one-half pound female infant was born in June, 1957. In July, 1957, the 6-mercaptopurine was discontinued. To date the patient

continues in clinical remission, and her child is completely healthy.

Case 2. This 29 year old white woman had had an uneventful pregnancy until the third trimester, at which time she noted ease of fatigue, ease of bruising, and mild gingival bleeding. A hemoglobin of 6.0 gm. and a white blood cell count of 3,500 were noted by her family physician. During the eighth month of gestation, after an inadequate response to liver and iron, she was transfused with six units of whole blood. A few weeks later, because of recurrence of her anemia, labor was induced and she delivered a normal female infant. The patient did well until 12 days postpartum, at which time vaginal bleeding occurred, requiring a dilatation and curettage. She was then transferred to University Hospital for evaluation of her anemia and bleeding.

Physical examination was unremarkable except for a few fading ecchymoses on

the left foot.

Laboratory studies revealed: hemoglobin, 11.9 gm. (76%); red blood cells,  $4.0 \times 10^6$ /mm.<sup>3</sup>; hematocrit, 33 vol.%; white blood cells, 1,350/mm.<sup>3</sup>, with a differential of polymorphonuclears, 34%; large lymphocytes, 45%; small lymphocytes, 15%; monocytes, 3%; eosinophils, 3%. Platelets were present in normal numbers. Urine, nonprotein nitrogen, fasting blood sugar, uric acid and liver function studies were within normal limits. The initial marrow obtained was hypercellular, with an erythrocyte: granulocyte ratio of 1:5 and grossly disturbed granulopoiesis, with large atypical progranulocytes and myelocytes, and an increase in the number of blast forms and hemohisticcytes. This marrow was interpreted as indicative of either a toxic process or possibly an early, acute leukemia.

Initial therapy consisted only of supportive measures. Despite blood transfusions the hemoglobin continued to fall, and progressive deterioration was evident. A repeat bone marrow examination two and one-half months later again demonstrated hypercellularity, with further depression of erythropoiesis and grossly abnormal granulopoiesis. The erythrocyte: granulocyte ratio was 1:30, and the majority of the cells of the granulocytic series were in the blast-to-progranulocyte stage, with marked monocytoid changes. A diagnosis of acute myelomonocytic leukemia was

made.

The clinical course continued downhill. A patchy bronchopneumonia responded suboptimally to antibiotics. During the last month of the patient's life the administration of 200 mg, of hydrocortisone per day resulted in no apparent change in the course of her progressive deterioration, and she died six months post partum.

Autopsy corroborated the diagnosis of acute myelomonocytic leukemia, with extensive infiltration of spleen, liver, lymph nodes, lungs, gastrointestinal tract,

uterus, skin and diaphragm. Bilateral intracerebral and subdural hemorrhages were

Case 3. This 24 year old white woman had been well until two months prior to her admission, at which time she had noted the onset of ease of fatigue, weakness and ease of bruising, and recent amenorrhea. She was seen by her family physician, who made a diagnosis of pregnancy of two to three months gestation. No abnormal physical findings were noted. Her symptoms became progressively more severe, and at about five months gestation she developed fever, night sweats, and a tender swelling in the right side of the neck. An abnormal white blood count was noted by her family physician, and she was referred to University Hospital.

Physical examination on admission revealed a pale, acutely and chronically ill white woman with multiple discrete, tender, 1 cm. bilateral anterior cervical lymph nodes, a markedly tender sternum, and ecchymoses over the lower extremities. The liver and spleen were not palpable, and the uterus was palpated at the level of the umbilicus. Obstetric examination revealed that the fetus was not viable.

Laboratory studies revealed: hemoglobin, 7.8 gm.; red blood cells,  $2.8 \times 10^{\rm s}/$  mm.³; white blood cells,  $80,000/{\rm mm.}^3$ , with a differential of polymorphonuclears, 35%; large lymphocytes, 1%; progranulocytes, 20%; blasts, 44%, some of which contained Auer's rods. Platelets were moderately decreased. Liver function and other routine studies were within normal limits except for 2 plus albumin in the urine and a non-protein nitrogen of 44. Bone marrow aspiration yielded a diffusely hypercellular specimen, with only rare megakaryocytes and a few normoblasts. About 90% of the cells were large, atypical blasts and early progranulocytes. A diagnosis of acute granulocytic leukemia was made.

The patient was treated with whole blood and ACTH gel, 30 units intramuscularly twice a day. Rapid deterioration occurred, and she developed a bilateral pneumonitis which failed to respond to antibiotics and died less than one month after admission.

At autopsy there were massive leukemic infiltrates throughout both lungs, with an associated bacterial pneumonitis. Prominent leukemic infiltrates were also noted in the lymph nodes, spleen and liver. No abnormality or evidence of leukemia was noted on examination of the fetus at postmortem examination.

Case 4. This 24 year old white female had been well until three months prior to admission, when she first noted the onset of fatigue, malaise and anorexia. Over the next two months she noted a progression of these symptoms, as well as pallor, exertional dyspnea and a 21-pound weight loss. The patient was aware of being pregnant, and finally consulted her family physician, who referred her to University Hospital.

Physical examination on admission revealed an acutely ill, pale, obese woman. There was slight sternal tenderness. The liver was palpable 2 cm, beneath the right costal margin. There was an ulcerated lesion on the right labia majora, with a severe cervicitis, and a gravid uterus compatible with five months gestation.

Laboratory studies on admission revealed: hemoglobin, 8.4 gm. (54%); red blood cells,  $3.0 \times 16^6/\text{mm.}^3$ ; hematocrit, 26 vol.%; white blood cells,  $10,550/\text{mm.}^3$ , with polymorphonuclears, 12%; blasts, 88%. The platelets were moderately reduced in number. Urinalysis revealed 1 plus albuminuria and 8 to 10 white blood cells per high power field. The fasting blood sugar, nonprotein nitrogen, liver function studies, electrolytes and chest film were all within normal limits. The initial bone marrow aspiration revealed a very hypercellular specimen, with 95% of the cells of the hemocytoblastic type, some with a tendency toward granulocytic differentiation. A diagnosis of acute granulocytic leukemia was made.

The patient was placed on hydrocortisone, 200 mg. per day, antibiotics, and routine supportive measures, including multiple transfusions. The white count

promptly declined to leukopenic levels (in the range of 1,350 to 1,500/mm.³). Approximately three weeks after the institution of steroids, 6-mercaptopurine was begun, in a dosage of 150 mg. per day. Clinically, improvement was marked, but only partial hematologic remission was achieved. The patient was discharged to her home

on 75 mg. of 6-mercaptopurine and 20 mg. of prednisone per day.

Four months after institution of the 6-mercaptopurine the patient had a normal, spontaneous delivery of a female infant who was and is well to date, at the age of two years. Following the delivery the mother had a sudden exacerbation of symptoms and a rise in white blood cells to 11,250/mm.³, with an increase in percentage of blasts to 34. The 6-mercaptopurine was increased to 200 mg. per day, but her clinical and hematologic response was suboptimal. The 6-mercaptopurine was discontinued, and she was begun on Methotrexate, 2.5 mg. per day. Prednisone was continued.

The patient did fairly well on this program until approximately seven months post partum, when she had the sudden onset of fever, chills, malaise and hematuria. On examination there was marked hepatosplenomegaly. Petechiae and purpura were prominent. Pneumonitis of the left upper lobe was evident on physical examination as well as on chest x-ray. Blood cultures grew out *Pseudomonas aeruginosa*. Multiple septic emboli were noted in the skin. Energetic antibiotic therapy failed to affect the course of events, and the patient died seven months post partum and 11½ months after diagnosis.

Autopsy revealed acute granulocytic leukemia infiltrates of the liver, spleen, kidneys and lymph nodes. Pulmonary hemorrhage was present, as was glomerulonephrosis. No gross or microscopic abnormalities of the ovaries, tubes or uterus

were noted.

Case 5. This 27 year old white woman was in her sixth month of gestation when she began to note spontaneous bruising, gingival bleeding, progressive ease of fatigue and weakness. The patient was seen by her family physician who, following an examination of her peripheral blood, made a diagnosis of acute monocytic leukemia and referred her to University Hospital.

Physical examination on admission revealed an acutely ill woman, with multiple abdominal and lower extremity petechiae and ecchymoses. Gingival hypertrophy with marked friability was present. Moderate sternal tenderness was noted. The liver and spleen were not palpable. The enlarged uterus was consistent with a

seven-month intra-uterine pregnancy.

Laboratory examination on admission revealed hemoglobin, 7.3 gm. (47%); red blood cells,  $2.1 \times 10^6/\text{mm.}^3$ ; hematocrit, 21 vol.%; white blood cells,  $3,400/\text{mm.}^3$ , with polymorphonuclears, 6%; large lymphocytes, 8%; small lymphocytes, 10%; monocytes, 45%; promonocytes, 4%; monoblasts, 25%; histiocytes, 2%. Three nucleated red blood cells per 100 white blood cells were present. The platelets were virtually absent. The bleeding time (Ivy) was over 20 minutes, and the clotting time (Lee-White) was 11 minutes. Prothrombin concentration was 43%. The urine, nonprotein nitrogen, uric acid, fasting blood sugar, liver and renal function studies, and electrolytes were within normal limits. Sternal aspiration revealed a hypercellular specimen. No megakaryocytes were present. Approximately 95% of the cells were monoblasts. Normal granulopoiesis was virtually absent, and erythropoiesis was very scanty. A diagnosis of acute monocytic leukemia was made.

The patient was treated supportively, and given blood as well as methyl prednisolone 48 mg. per day. Initially she showed some clinical improvement, but then manifested increasing bleeding tendencies. In spite of fresh whole blood, vitamin K and platelet transfusions, she lapsed into a lethargic state on the fourth hospital

day, which progressed to coma and death on the sixth hospital day.

A postmortem cesarean section was performed, yielding an apparently normal

3 pound, 7 ounce female infant with normal hematologic values. The child did well for the first three days of life, and then suddenly showed a marked change in vital signs, characterized by progressive tachycardia, tachypnea and low grade fever, and died. Autopsy examination revealed no overt cause of death. No abnormality of the hematopoietic tissue was noted.

Autopsy examination of the mother revealed monocytic leukemic infiltrates of the lungs, liver, spleen and lymph nodes. The cause of death was massive subdural, subarachnoid, intracerebral and pontine hemorrhage. No leukemic infiltrates were identified in the female genital tract.

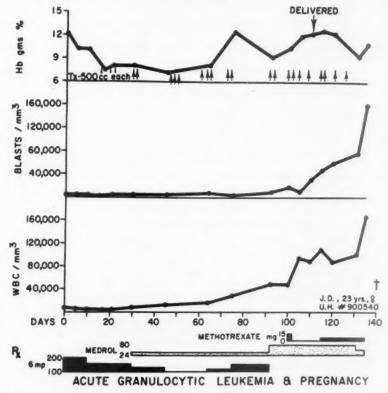


Fig. 2. Case 6. Acute granulocytic leukemia and pregnancy in a 23 year old woman.

Case 6 (figure 2). This 23 year old white woman entered with a history of known pregnancy of five months gestation. For two months prior to admission she had noted recurrent oral ulcerations, weakness and postural dizziness. Some ease of bruising had been present during the month prior to admission. The patient had been hospitalized elsewhere with a diagnosis of anemia, which responded poorly to iron and vitamin  $B_{12}$ .

Physical examination on admission revealed a well developed, well nourished woman with petechiae over the oral mucosa, trunk and lower extremities. Moderate

sternal tenderness was present. The liver and spleen were not palpable, there was no significant peripheral adenopathy, and the uterine enlargement was consistent

with a five months pregnancy.

Laboratory examination revealed: hemoglobin, 12.3 gm. (79%); red blood cells, 4.2 × 10<sup>6</sup>/mm.<sup>3</sup>; hematocrit, 37 vol.%; white blood cells, 7,650/mm.<sup>3</sup>, with a differential of polymorphonuclears, 4%; large lymphocytes, 17%; small lymphocytes, 20%; monocytes, 12%; progranulocytes, 1%; blasts, 46%. Platelets were markedly reduced in number. Sternal aspiration revealed a hypercellular specimen, with 70% of the cells atypical myeloblasts, some of which had a monocytoid character. Megakaryocytes were reduced, and erythropoiesis was scanty. A diagnosis of acute subleukemic granulocytic leukemia was made (figure 2).

The urine, blood urea nitrogen, fasting blood sugar, uric acid, liver function studies and electrolytes were within normal limits. Serum electrophoresis revealed a slight elevation of beta globulin but was otherwise unremarkable. The prothrombin

concentration was 66%.

The patient was placed on 6-mercaptopurine (5 mg. per kilogram), 325 mg. per day. Significant clinical response was noted in approximately one week, and the 6-mercaptopurine was slowly tapered to 50 mg. per day. Following one month of therapy, hemorrhagic manifestations became prominent, and methylprednisolone, 24 mg. per day, was instituted. The patient had a partial remission and was discharged to her home on 6-mercaptopurine, 50 mg. per day, and methylprednisolone, 24 mg. per day. The patient did well at home for over two months, but then noted a recurrence of her constitutional symptoms and, on examination, was noted to have marked sternal tenderness and hepatosplenomegaly. The white blood count rose to the 40,000/mm.³ range, with an increased number of blasts. The 6-mercaptopurine was discontinued, and she was given a single oral dose of Methotrexate, 15 mg., and the methylprednisolone was increased to 80 mg. per day. Ten days later she had the onset of spontaneous labor, and delivered a normal 5-pound, 4-ounce baby girl without complications. The infant was clinically and hematologically normal.

Following the delivery the patient manifested progressive deterioration, with weight loss, fever, bone pain and progressive hepatosplenomegaly. She was placed on Methotrexate, 2.5 mg. per day, but continued her downhill course and died four weeks post partum. The baby is doing well and is normal at 17 months of age.

Case 7 (figure 3). This 28-year old white woman had been essentially well until two months prior to admission, at which time she noted weakness, fatigue and amenorrhea. The diagnoses of pregnancy and anemia were made. Iron was given, without benefit. During the next two months she noted progression of her constitutional symptoms, a 7-pound weight loss and ease of bruising. Sternal aspiration was performed at another hospital. The diagnosis of leukemia was made, and the patient was transferred to University Hospital.

Physical examination on admission revealed a thin, pale woman with palpable, discrete, small bilateral posterior cervical, submandibular and bilateral axillary lymph nodes. Moderate sternal tenderness was present. The liver and spleen were not palpable. The uterus was compatible with a six months pregnancy. Multiple ec-

chymoses were present over both lower extremities.

Initial laboratory studies revealed: hemoglobin, 6.0 gm.; hematocrit, 17 vol.%; white blood cells, 41,250/nm.³, with a differential of polymorphonuclears, 14%; metamyelocytes, 16%; myelocytes, 6%; progranulocytes, 16%; myeloblasts, 48%, many of which contained Auer's rods. Platelets were moderately decreased. The urine revealed a trace of albumin, and 13 to 15 white blood cells per high power field. The serum uric acid was 3.5 mg.%. The remainder of the laboratory studies were within normal limits except for a fibrinogen assay of 160 mg.%. Sternal aspiration revealed only rare megakaryocytes, and an erythrocyte: granulocyte ratio of 1:18.

Myeloblasts were increased in number (45%), and Auer's rods were noted. Many of the cells had monocytoid characteristics. The diagnosis of acute myelomonocytic leukemia was confirmed.

The patient was started on 6-mercaptopurine (5 mg./kilogram), 250 mg. per day, and tolerated the dosage well. As she became leukopenic the dosage was tapered to 100 mg. per day. Three weeks later she went into spontaneous labor and delivered a premature baby girl weighing 3 pounds, 8 ounces. The infant was hematologically and otherwise normal, and has done well to date, at six months of age.

The mother did well until 96 hours post partum, when she had the onset of profuse vaginal bleeding. Dilatation and curettage were performed and some re-

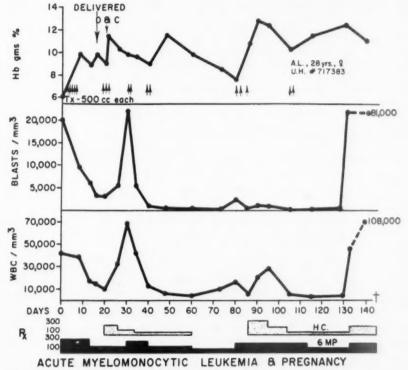


Fig. 3. Case 7. Acute myelomonocytic leukemia and pregnancy in a 28 year old woman.

tained placenta was removed, but she continued to have significant uterine bleeding, and petechiae and purpura were noted, followed shortly by a rising white blood count and an increasing number of blasts (figure 3). The fibrinogen assay was 290 mg.%. The patient was treated with fresh blood, 2 gm. of fibrinogen and platelet packs, and was started on hydrocortisone, 200 mg. per day. The 6-mercaptopurine, which had been withheld for five days following institution of labor, was re-instituted at the level of 100 mg. per day.

The patient slowly responded, and progressed to partial remission. The hydrocortisone was gradually withdrawn, and she was maintained on 6-mercaptopurine, 50 mg. per day. Three months post partum, on a routine clinic visit, new ecchymoses were noted, as well as a fall in hemoglobin and an increase in white blood count and percentage of blasts. The patient was re-admitted, and an added feature at this time was massive pharyngeal infiltration, with neoplastic obstruction of the eustachian tubes. Local irradiation was directed to the posterior pharynx, and the 6-mercaptopurine was increased to 175 mg. per day. The patient again had a partial remission, and was discharged to her home on 100 mg. per day of 6-mercaptopurine.

Four months post partum the patient developed sudden left upper quadrant pain, and was re-admitted because of possible impending rupture of the spleen. Examination revealed marked left upper quadrant tenderness. The spleen was palpable 5 cm. beneath the left costal margin. Showers of peternae were noted. No friction rub was heard. Hydrocortisone was reinstituted, but the patient died

72 hours after admission.

At autopsy, leukemic infiltrates of the lungs, liver, spleen, lymph nodes and intestine were noted. The spleen showed old and recent infarctions, but there was

no evidence of rupture or subcapsular hemorrhage.

Case 8. This 16 year old white girl was referred to University Hospital with diagnoses of pregnancy of two and one-half months gestation, and leukemia. Three weeks prior to admission she had noted the onset of spontaneous bruising, daily fever and an episode of epistaxis.

Physical examination on admission revealed a well developed, well nourished white girl with scattered ecchymotic areas on the thighs and lower extremities. The retinae showed a few flame-shaped hemorrhages. Several small bilateral axillary nodes were present. The liver and spleen were not palpable, and the uterine enlargement was compatible with a pregnancy of four and one-half months gestation.

Laboratory studies revealed: hemoglobin, 8.9 gm.; hematocrit, 28 vol.%; white blood cells, 53,000/mm.³, with a differential of polymorphonuclears, 25%; large lymphocytes, 27%; monocytes, 20%; eosinophils, 2%; myelocytes, 3%; progranulocytes, 1%; blasts, 22%; normoblasts, 2 per 100 white blood cells. The bleeding time (Ivy) was one minute, and the clotting time (Lee-White) was 10 minutes. Prothrombin concentration was 23%. Fibrinogen assay on admission was too low to measure. The patient was given 2.4 gm. of fibrinogen, and at "zero" time (i.e., immediately after administration), a normal clot formed. At three hours the fibrinogen level was 60 mg.%, and at 24 hours it was 45 mg.%. The blood urea nitrogen, urine, serum uric acid, liver function studies and chest film were within normal limits. A slight increase in serum beta globulin was noted on paper electrophoresis. Sternal aspiration established the diagnosis of acute erythroleukemia.

The patient was extremely uncooperative and hostile. Because she repeatedly threatened to leave the hospital, and did so counter to medical advice on the twelfth day, her treatment was limited to blood transfusions and prednisone, 60 mg. per day.

No significant change in her status was noted.

She discontinued her steroid 10 days after leaving the hospital. She was seen again two months later, with essentially the same findings except that the uterus was enlarged to that of a seven months pregnancy. The patient again refused medical care and hospitalization. During the eighth month of gestation she went into spontaneous labor at home, was admitted to a local hospital, and delivered spontaneously a stillborn female infant. She died two hours later. No autopsy was performed.

#### COMMENTS

Table 1 represents a compilation of our cases in chronologic order of their presentation. Of interest is the fact that, of this group, only two were primiparous. Allen 10 has stated that acute leukemia is seen in the nulli-

parous patient and chronic leukemia in the multiparous patient. No such relationship can be substantiated, either in our cases or on review of the literature.<sup>6, 11-14</sup>

Our patients showed considerable variation in age and in the type of acute leukemia, with a notable absence of acute lymphocytic leukemia.

Variation can also be noted in the month of gestation during which symptoms referable to leukemia were first noted. Despite the fact that most of these patients were under medical care because of pregnancy, there was a two- to three-month lag between the onset of symptoms of leukemia and the diagnosis. A recurring history was that of the patient's having

Table 1
Compilation of Cases in Chronologic Order of Presentation

			Month of Gestation				Results		
Case	Age	Parity	At On- set of Symp- toms	At Diagnosis	Type of Leukemia	Therapy	Mother	Infant	
1	29	Pi Gi	dated	emia ante- pregnancy 21 yrs.	Acute stem cell	6—M.P.	Complete remission	Normal female, 21 yrs. of age	
2	29	Piv Giv	8	3 wks. post partum	Acute myelomono- cytic	Hydrocortisone	Died 6 mos. post partum	Normal female, 5 yrs. of age	
3	24	Pi Gii	2	5	Acute granulocytic	ACTH	Died 5th month of gestation	Dead fetus	
4	24	Pa Gi	3	5	Acute granulocytic	6—M.P., Prednisone	Died 7 mos. post partum	Normal female, 2 yrs. of age	
5	27	Pii Giii	6	7	Acute monocytic	Methyl- prednisolone	Died 7th month of gestation	Female infant, died at 3 days	
6	23	Pi Gii	3	5	Acute granulocytic	6-M.P., Methyl- prednisolone, Methotrexate	Died 1 month post partum	Normal female, 1 yr. of age	
7	28	Pii Giv	3	6	Acute myelomono- cytic	6—M.P., hydrocortisone	Died 4 mos. post partum	Normal female, 6 mos. of age	
8	16	Po Gi	2 5	4	Erythro- leukemia	Prednisone	Died during delivery, 8 mos. gestation	Female, stillborn	

been treated for "anemia" by means of various hematinics, while the initial nonspecific constitutional symptoms were ascribed to the pregnancy. The usual fulminant course of acute leukemia, however, soon brought the correct diagnosis to the forefront.

Two maternal deaths occurred before term. One patient (case 8) died during delivery at another institution three months after diagnosis of erythroleukemia. Four patients succumbed to their leukemia between one and nine months post partum. One patient is still alive and in complete remission five years after diagnosis.

Five living, healthy babies resulted from these pregnancies and, inter-

estingly enough, all of the infants were female. No congenital abnormalities were noted, and no cases of blood dyscrasia have been seen in any of these babies. Case 5 had a postmortem cesarean section, with delivery of an apparently normal, albeit premature, infant that lived only three days. At autopsy of the infant, no specific cause of death was found and no evidence of leukemia was present.

Fibrinogen levels in our two most recent patients were markedly reduced, confirming the observations of Yahia et al.<sup>5</sup> that the fibrinogen levels in patients with acute leukemia and pregnancy were reduced from the level anticipated at that stage of gestation. Case 8, the 16 year old girl with erythroleukemia, had a fibrinogen level of zero, and upon administration of fibrinogen she failed to maintain an effective level for more than a few minutes.

From a therapeutic point of view, case 1 is of particular interest because she conceived while on 50 mg. of 6-mercaptopurine, and continued on this dosage virtually throughout her entire pregnancy without untoward effect upon the child.

#### Discussion

The effect of pregnancy on the survival and longevity of leukemic patients has been controversial. Some authors feel that pregnancy has a definitely deleterious effect and shortens life expectancy. 15, 16, 39 That this concept is still current in some quarters is evidenced by Miasnikov's 39 recent article in the Russian literature reporting three cases of leukemia and pregnancy, two chronic and the third a case of acute chloroma, in which he felt pregnancy aggravated the leukemia. The survival time of his patients was short, but it should be noted that none received specific antileukemic therapy. His conclusion is that "termination of pregnancy is indicated in leukemia at as early a stage as possible." The more common current feeling, and one to which we subscribe, is that pregnancy exerts no specific effect per se on the course of the acute leukemia. 1, 4, 6, 14, 17, 38, 40 except insofar as early gestation imposes an obstacle to vigorous treatment of the leukemia. Birge et al.18 in 1949 described a case of acute leukemia where a spontaneous remission of 21 months' duration occurred, with the onset of the remission during pregnancy. However, increased fetal mortality and abnormality in acute leukemia are well recognized.19

The question of transmission of leukemia is an unresolved problem which is of special interest in instances of leukemia and pregnancy. A point of controversy has been raised by the work of Gross, <sup>21, 22</sup> who has demonstrated that lymphatic leukemia in mice of the AK strain can be transmitted from generation to generation by administration of cell-free extracts of leukemic organs to mice in the suckling stage. This study has been used to support the viral etiology of leukemia, and suggests a high susceptibility to induced leukemia in the neonatal period, from which it might also be implied in the prenatal period; and yet there has been no report of a leukemic newborn

delivered of a leukemic mother (either acute or chronic leukemia), although there have been cases of leukemic newborns delivered of hematologically normal mothers. <sup>24, 25, 26, 27</sup> Burchenal's animal studies <sup>20</sup> afforded compelling experimental evidence corroborating the clinical impression that the placenta serves as a barrier in this disease. Furthermore, well over 200 attempts to transmit leukemia from one human to another have failed, <sup>28–30</sup> including the carefully performed cross-circulation studies of Bierman and his group. <sup>28</sup>

This does not, however, rule out the possibility of hereditary transmission of the disease. Bierman <sup>28</sup> has commented on the need for the collection of data and long-term follow-up of the infants delivered of leukemic mothers in order to aid in the eventual delineation of the role of heredity in the transmission of leukemia. This is emphasized by the recent report of Cramblett et al., <sup>31</sup> recording the development of leukemia at nine months of age in an infant born of a mother who had the onset of her clinical symptoms of leukemia at about seven months gestation. Both mother and child had acute lymphocytic leukemia. The child had been clinically and hematologically normal prior to nine months of age.

With the advent of specific antileukemic therapy the treatment of pregnant leukemia patients has undergone many changes. The management of such patients can be divided into two facets. The first, and generally simplest, is that of the obstetric care. This should be in the nature of the good obstetric principles applicable to any pregnancy. Since evidence is lacking that pregnancy has a deleterious effect on acute leukemia, and since, as Allen <sup>10</sup> has noted, the stress of interruption of the pregnancy can be just as great as the stress of parturition, no indication exists for the interruption of the pregnancy. However, the obstetrician must be alert to the possible need for emergency cesarean section in these patients in the event of rapid deterioration or death prior to delivery.

Effective management of the leukemia requires the close coöperation of the patient and frequent follow-up by the physician. Routine supportive measures, such as blood and antibiotics, should be employed as needed. The question of specific antileukemic therapy is perhaps somewhat more controversial. Dameshek states that "one's therapeutic efforts should be limited to relatively gentle procedures, such as the use of transfusions, the administration of relatively small doses of prednisone (we have used 25–50 mg. daily), antibiotics, and other symptomatic care." <sup>40b</sup> Other authors <sup>5, 13, 38</sup> express similar sentiments. It is our observation, however, that specific antileukemic therapy is beneficial and can be initiated safely after the first trimester of gestation. The consideration of stage of gestation is imposed by the observation of fetal abnormalities in experimental animals <sup>34, 36, 36</sup> and in humans when therapeutic doses of antimetabolites have been employed during the early stages of gestation. That such abnormalities do not necessarily attend the administration of small doses of

antimetabolites is suggested by our first patient (figure 1, table 1), who was on 50 mg. of 6-mercaptopurine during her entire pregnancy, with no abnormalities noted in the child. Furthermore, antimetabolites were also employed in cases 4, 6 and 7 at varying times beyond the first stage of gestation, with no abnormalities in the children. Others 37 have also used such specific therapy, with no untoward results. Our feeling is therefore that antimetabolites are relatively safe, useful and indicated in acute leukemia any time after the first trimester. Steroids are useful where bleeding, hemolysis or severe toxicity is a prominent clinical feature.

Another consideration of prime importance in the management of these patients is the presence of hypofibrinogenemia at the time of parturition. As pointed out by Yahia et al., and corroborated by our most recent cases, hypofibrinogenemia can contribute to the problem of bleeding. Suitable laboratory studies during pregnancy will alert the team of internist and obstetrician to prepare for the correction of the deficiency when necessary. In itself, the thrombocytopenia that most of these patients manifest is not ordinarily associated with major bleeding problems at the time of delivery, but when thrombocytopenia is coupled with low fibringen levels there may

be serious and fatal hemorrhage at parturition.

The immediate postpartum period requires close observation of the patient. Many of the previously recorded cases reveal rapid deterioration immediately after delivery, with early death. This has been observed in both the steroid- and nonsteroid-treated patients. Because of this threat post partum, close scrutiny is necessary and active antileukemic therapy indicated. The combination of antimetabolites and massive doses of steroids may be required to reverse such deterioration. Iavorkovskii et al.38 especially emphasize the need for steroids in such instances, based on the observations that hypertrophy of the anterior lobe of the pituitary and of the cortical layer of the adrenals occurs in pregnancy, associated with a rise in the blood and urinary levels of 17-hydroxycorticosteroids after the first trimester to two to five times normal values, and with a notable fall from this level during the first postpartum week.

Sudden death of the infant during the neonatal period has been noted previously,33 and was observed by us in case 5 (table 1) of this series. Correlation has been made between this pattern of rapid deterioration and death in the first 96 hours of life of the infant and the previous management of the leukemic process with adrenal steroids in the mother. Morgan and Reyes 33 present a case where this course of events was reversed upon ad-

ministration of steroids to the infant.

The question of need for supplemental steroids in such infants raises the problem of the complexity of the metabolism of hydrocortisone during pregnancy.41 Migeon et al.42 studied the placental passage of 17-hydroxycorticosteroids, and found that hydrocortisone passes from the maternal to the fetal circulation via the placenta in relatively constant ratios. Thus the administration of steroids or the increased stress in leukemic mothers may affect the infant in the early neonatal period. Gardner <sup>41</sup> states: "The developing fetus biosynthesizes essentially no cortisol (Hydrocortisone)"; also: "The newborn is not able to raise its own plasma concentration of cortisol (Hydrocortisone) to visible levels until several days of life have passed." The need for and the value of steroids in these infants should therefore be borne in mind, especially since the deterioration of the infant, once established, is rapid and relentless.

#### SUMMARY

Eight cases of acute leukemia and pregnancy seen during the last five years are presented and discussed.

A plan for the independent management of the pregnancy and the leukemia, with close coöperation between obstetrician and internist, is advocated.

The use of specific antileukemic therapy, in the form of antimetabolites after the first trimester of pregnancy, is believed to be of value. The adjuvant use of steroids is recommended where bleeding or toxicity is a significant feature. During the early postpartum period the potential need for steroids in both the mother and the infant should be borne in mind.

Growing recognition of hypofibrinogenemia in such cases warrants investigation and proper preparation in every case.

#### SUMMARIO IN INTERLINGUA

Le reportate casos de co-occurrentia de leucemia acute e pregnantia es si pauco numerose que on poterea concluder que le curatela de tal patientes es infrequentemente un question de interesse clinic. Tamen, in le curso del passate cinque annos nos ha incontrate octo gravidas con leucemia acute. In septe le diagnose esseva primo establite post le declaration del pregnantia. In un, le diagnose de leucemia acute, sequite per un remission therapeutic, precedeva le pregnantia per duo annos. Le serie include nulle caso in que le conception occurreva in recognoscite sed non stabilisate leucemia acute.

Le casos es discutite in detalio. A parte le mesuras supportative—i.e. transfusiones, antibioticos in tanto que indicate, etc.—omne le patientes recipeva un therapia active visante a reprimer le leucemia. Esseva usate, pro iste objectivo, 6-mercaptopurina, Methotrexato, e adrenocorticosteroides, sol o in combination, con le debite respecto pro le ben-esser del matre e etiam del feto. Le phase del gestation e le stato del matre esseva considerate como importante in le selection del un o del altere del mentionate agentes.

Esseva vidite tres mortes materne ante le parturition. Cinque normal vivenatos ha resultate ab iste pregnantias. Nulle monstros e nulle caso de dyscrasia sanguinee esseva trovate inter le infantes. Es presentate le problema de hypofibrinogenemia in leucemia acute e pregnantia. Un del patientes in iste serie vive al tempore presente, trovante se in remission cinque annos post le diagnose.

Super le base de nostre observationes nos conclude que—a parte le currentemente disponibile mesuras supportative—agentes antileucemic pote esser usate durante le pregnantia al beneficio de matre e de feto. Pregnantia per se non exerce un effecto

exacerbatori super le curso de leucemia acute. Le uso adjuvante de steroides es recommendate in casos in que sanguination o toxicitate es un factor de importantia. Es sublineate le necessitate del uso de steroides tanto pro le matre como etiam pro le infante durante le prime periodo post parto. Le crescente recognition del rolo de hypofibrinogenemia in tal casos justifica le investigation e le appropriate preparation de omne caso individual.

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## CHEMOTHERAPY OF ADRENOCORTICAL CANCER WITH o,p'DDD \*

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Our approach to the chemotherapy of adrenocortical carcinoma is based upon the original observations of Nelson and Woodard.<sup>1</sup> They observed that the oral administration to dogs of the insecticide, DDD, or Rothane, induced a selective necrosis of the zona fasciculata and zona reticularis of the adrenal cortex. Nichols and his associates 2, 3 pursued this finding and demonstrated that adrenal cortical function was markedly diminished in dogs so treated. However, early attempts to apply this adrenocorticolytic effect in man were unsuccessful.4,5,6

Further exploration of the therapeutic potential of this compound was made possible by the observations that a contaminant of the crude DDD, the ortho, para prime isomer (figure 1), is an effective adrenocorticolytic agent,7,8,9 and that para para prime, DDD, the major constituent of Rothane, is inactive. This finding gave fresh impetus to our attempts at management of patients with metastatic adrenocortical carcinoma, and our initial observations have been reported.10, 11

During the last two years we have been able to evaluate the response of 18 patients with metastatic adrenal cancer to o,p'DDD. This extended experience permits an assessment of the effects of therapy, and has suggested certain procedures in the treatment of these patients.

#### METHODS

The o,p'DDD was prepared by fractional recrystallization from the crude DDD.‡ The drug has been given orally, either in 0.5 gm. capsules, or in tablets, in divided doses throughout the day. Most patients received 10 gm. of o,p'DDD daily until either significant remission was achieved or the limit of tolerance was reached. Initially, we instituted treatment with low doses of o,p'DDD, gradually increasing the level to 10 gm. daily. More recently, however, we have started therapy with 10 gm. daily, without

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<sup>†</sup> Deceased. Dur material was obtained from the Edcan Chemical Company, Norwalk, Connecticut,

and through the Cancer Chemotherapy National Service Center. Requests for reprints should be addressed to Mrs. Olga Collier, Building 10, Room 12-N-202, National Cancer Institute, Bethesda 14, Maryland.

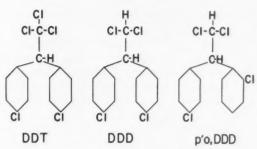


Fig. 1. Structure of o,p'DDD and related insecticides.

noticeably altering the tolerance. When possible, we have continued the high dose level of o,p'DDD for several weeks after regression of disease was noted. The dose was then decreased to from 2 to 4 gm. daily if gastro-intestinal tolerance permitted. The patients received other medications as indicated, particularly promazine derivatives for the control of nausea. Prednisone or dexamethasone was used when urinary corticoid excretion had fallen to low levels and when there were signs of adrenocortical insufficiency.

The urinary excretion of 17-hydroxycorticoids and 17-ketosteroids was measured at least three times weekly. The ketosteroids were determined using a micro modification of the method of Werbin and Ong,<sup>12</sup> and the corticoids by the method of Silber and Porter.<sup>13</sup> The excretion of dehydro-

TABLE 1 Status of Patients

Patient	Age. Yrs.	Sex	Average 17-KS	Initial 17-OHCS	Virilization	Cushing's Syndrome	Site of Metastase
FOX (A)	56	F	250	25	+	+	LA
FOX (B)	57	F	35	12	+ 1	+	LA
STR	57	F	50	15	+ 1	+	L
VEI (A)	33	F	60	30	+	+	A
VEI (B)	34	F	90	20	+	+	A
SHER	36	F	60	70	+ 1	+	A
NIR	55	F	30	10	+ 1		LA
CHER	38	F	600	170	+ 1	+	A
MAL	38	F	50	12	+	+	LA
IOZ	11	F	40	170	+	1	LA
FIS	58	F	162	30	+	1	A
HIL	36	F	60	23		+	A
HOP	14	M	150	1		1	A
SCH	17	M	30	5	I		T
ALE	o l	M	80	2			A
HOM	52	M	25	8	T		LA
VIC	59	M	14	6			
		M					A
SMI	56	F	110	20			A L
CLA	51		22	8			
RIC	50	F	110	45	+	+	LA

L = lung; A = abdomen

epiandrosterone was estimated by the Allen reaction after solvolysis with ether.<sup>14</sup>

Complete blood counts, including platelets and reticulocyte counts, were performed twice weekly. Liver function tests, urinalyses and serum creatinine levels were obtained weekly. Electroencephalography was done on admission and at four- to six-week intervals during therapy.

We have used the term "regression" to signify measurable decrease of metastatic disease. In each instance, this has meant diminution in size of pulmonary or abdominal metastases. The term "steroid remission" indicates a sustained decrease in steroid excretion (to less than 70% of the initial levels). We have included in this compilation all patients treated with o,p'DDD except one girl who died of her disease soon after the initiation of therapy.

TABLE 2
Patients Showing Regression of Cancer

Patient No.	Site of Regression	Duration Intensive Therapy, mos.	Dose o,p'DDD During Intensive Therapy, gm.	Further Therapy, Daily Dose	Duration of Remission, mos.	Current Status
1	L	2	155	o,p'DDD, 3 gm. Prednisone, 5 mg. Florinef, 0.05 mg.	7	Slowly progressive
2 3	A	11	190	o,p'DDD, 5 gm.	11	Remission
3	A	1	183	Prednisone, 10 mg.	4	Dead
4	A	18	470	Prednisone, 2.5 mg.	26	Remission
5	L, A	2	500	Prednisone, 5 mg.	31	Remission
6A	L, A	4	890		5	Remission
6B	L	3	700	Prednisone, 7.5 mg.	2	Dead
- 7	L, A	4	774	o,p'DDD, 4 gm. Prednisone, 7.5 mg.	1 ½	Remission

All of the patients accepted for treatment had histologically proved adrenocortical carcinoma. Seventeen of the 18 had easily measurable metastases, and the remaining patient had clinical and biochemical manifestations of severe hyperadrenocorticism. Seventeen of the subjects exhibited elevated steroid excretion. These data have been summarized in table 1.

#### RESULTS

Regression of metastases was observed eight times in seven patients. The details of the dosage and duration of remission are set forth in table 2. The duration of intensive therapy (10 gm. daily) was as long as four months, and in several cases extended past the point when the first evidence of regression was noted.

The data presented in table 1 and figure 2 provide an over-all view of our observations to date. The findings in several cases will serve to illustrate certain features of the toxic and therapeutic effects observed.

#### DOSE OF OD'DDD V8 TUMOR RESPONSE

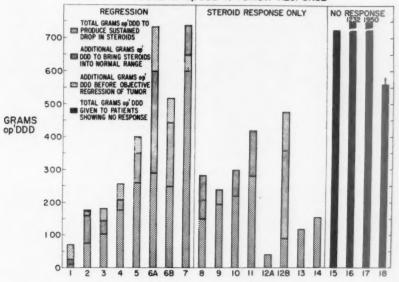


Fig. 2. Dose of o,p'DDD versus patient response.

#### CASE REPORTS

Case 1. A seven and one-half year old boy demonstrated the most rapid regression of pulmonary metastases that we have observed. After this regression had been maintained for seven months, a small increase in the size of one of the metastatic pulmonary nodules was noted, although the steroid excretion remained low and the patient was asymptomatic. This occurred in spite of maintenance doses of o,p'DDD of from 1 to 1.5 gm. daily. We have recently increased this to 3.0 gm. daily, with the hope of obtaining further regression.

Case 4. A three and one-half year old boy first received 0,p'DDD at the age of 18 months, at a daily dose of 1.0 gm. He exhibited substantial regression of a large abdominal mass, reduction in steroid excretion, and marked clinical improvement. He continued on this regimen for 18 months, with occasional brief interruptions because of anorexia or skin rash. At the end of this period, severe anorexia prevented further administration of the drug. In the subsequent eight months he has grown and gained weight, and presents neither clinical nor laboratory evidence of recurrent disease. Although this patient received a proportionately smaller daily dose of 0,p'DDD than did the adults, the duration of therapy was considerably longer.

Case 3. This patient died from septicemia following massive tumor necrosis, although significant regression of abdominal and pulmonary masses had occurred.

In figure 2 the relationship between the dose of o,p'DDD and the effects obtained has been diagrammed. Initial regression of tumors was usually observed from one to two weeks after the steroid excretion had reached normal levels. Of the seven patients classified as showing a steroid response only, case 11 had no measurable metastases but underwent un-

equivocal remission of hyperadrenocorticism. She was placed on a daily dose of 3.0 gm. of o,p'DDD but, despite continued therapy, developed an abdominal mass and recrudescence of Cushing's syndrome. She died in pulmonary edema 12 hours following an attempt at surgical excision of the recurrent mass.

Case 9 refused further therapy with o,p'DDD after the urinary steroids had become normal, and equivocal regression of pulmonary metastases had occurred. She remains free of symptoms. The other patients in this group have died, three of complications of the disease, one of a concurrent astrocytoma, and one of unknown cause. Three patients (cases 15, 16 and 17) died of adrenal carcinoma without evidence of significant response to o,p'DDD.

Some of the problems of therapy are apparent in case 6.

Case 6. In 1953 this 46 year old woman developed Cushing's syndrome with virilization. One year later, a left adrenal carcinoma was resected. In 1956 she received radiation therapy to the area because of recurrent Cushing's syndrome. This was ineffective and her disease progressed, eventuating in severe weakness, hypertension and congestive heart failure. In June, 1958, she was started on o,p'DDD. After she had received 800 gm. over a three-and-one-half-month period, there was regression of abdominal and pulmonary metastases (figure 3 a, b); the steroid excretion had fallen to normal range, and the Cushing's syndrome was no longer manifest. The drug was stopped at the end of September, 1958, because of gastrointestinal toxicity. By January, 1959, the excretion of 17-ketosteroids had increased; the patient was given 180 gm, of o,p'DDD over a period of six weeks, and the steroid excretion returned to normal. We attempted to give her a daily maintenance dose of o,p'DDD but she refused to take more drug at that time. By November, 1959, the patient was at her pretreatment status. Five hundred grams of o,p'DDD again caused regression of pulmonary metastases (figure 3 c, d), and the steroid excretion became normal. Hypertension persisted, however, and there was evidence of renal impairment. The patient subsequently developed septicemia associated with massive necrosis of abdominal metastases, and pulmonary edema, and died. Thus, although two distinct regressions were obtained in this patient, she could not tolerate enough o,p'DDD to prevent a recurrence of tumor growth.

The toxicity of o,p'DDD has been summarized in table 3. Anorexia and nausea were the most frequent and distressing problems. Lethargy and somnolence were often observed, but have been reversible on cessation of therapy or reduction in dose. Psychometric examinations were not substantially altered, even in patients who were lethargic when tested. The electroencephalograms in five instances were interpreted as indicating nonspecific deterioration. The absence of evidence of damage to kidney, liver or bone-marrow was noteworthy.

We have observed a syndrome that has occurred seven times in five patients with large abdominal metastases, consisting of abdominal pain, variable fever, a drop in plasma hemoglobin, occasionally with shock, and elevation of serum glutamic oxalacetic transaminase to as high as 1,400 units per milliliter. The autopsies of two patients who died with this syndrome revealed hemorrhage and infarction of large abdominal metastases.

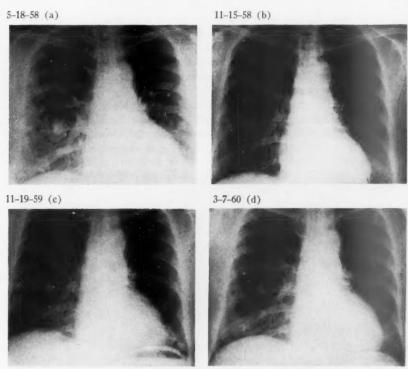


Fig. 3. Chest x-rays of case 6, who responded to two separate courses of o.p'DDD. a and b reflect the first course (900 gm. o.p'DDD); c and d reflect the second course (700 gm. o.p'DDD).

One of the episodes occurred in a patient who had received no o,p'DDD. Since this syndrome has not been commented on previously, however, it may be considered that the adrenocorticolytic effect of o,p'DDD can predispose to hemorrhage and infarction in the tumor mass.

Since all of our patients have had one remaining normal adrenal gland, we attempted to determine the effects of prolonged treatment with o.p'DDD

TABLE 3
Summary of Drug Toxicity

Type of Reaction	Number of Patient
Gastrointestinal	
Severe	3
Moderate	7
Mild	8
Skin rash	4
Central depression	
Severe	3
Mild	5
Muscular tremors	2

on the functional capacity of this gland. It is apparent that some patients had had prolonged suppression of function of the normal adrenal gland by the corticoids produced by the tumor. However, 40 to 80 units of cortrophin-zinc, given for periods from three to 18 days to four such patients after the corticoid excretion had become normal, elicited only one slight increase in steroid excretion.

In two additional patients the urinary 17-ketosteroids were high but the urinary corticoid excretion was normal. Thus, the function of the remaining adrenal gland was presumably normal and, in the one patient tested by the standard intravenous ACTH test, the plasma corticoids showed the

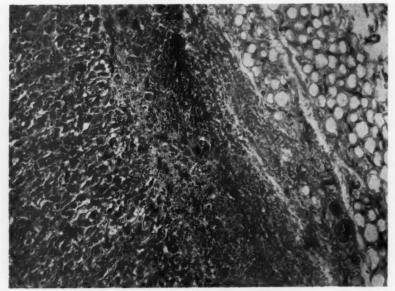


Fig. 4. Following administration of 1,950 gm. of 0,p'DDD, the adrenal cortex of this patient persisted as little more than an atrophic band between the capsule and the normal-appearing medulla (×117).

expected increase. After o,p'DDD therapy, neither of these patients responded to prolonged daily administration of cortrophin-zinc.

The changes in adrenal histology attributable to o,p'DDD are illustrated in figure 4. This is a photomicrograph of the most severely damaged adrenal gland in this series. The histologic changes resemble those reported in the dog, and consist of extensive destruction and fibrosis of practically all of the cells of the adrenal cortex. These effects differ from those associated with adrenal atrophy following prolonged suppression by excessive amounts of either endogenous or exogenous corticoids.

Since the zona glomerulosa of the dog adrenal cortex is relatively re-

sistant to o,p'DDD, we have examined the capacity to secrete aldosterone by the patient after treatment with o,p'DDD. Four patients whose steroids had been reduced to normal on therapy were subjected to sodium intake of only 14 mEq. daily for three days while receiving small doses of prednisone. The urinary sodium excretion decreased to below 10 mEq. daily in two patients, to 24 mEq. in the third, and did not decrease in the fourth. Although this procedure does not measure aldosterone directly, the impairment of the ability to retain sodium upon sodium restriction suggests that o,p'DDD had produced at least partial impairment of that portion of the adrenal gland involved in aldosterone secretión.

The steroid excretion of most of these patients fluctuated widely during the pretreatment periods. When the drug became effective, the rate of decrease of urinary 17-ketosteroids and of 17-hydroxycorticoids usually paralleled each other. However, in three subjects, urinary corticoid excretion reached normal or below normal levels before the urinary 17-ketosteroids were within the normal range. Dehydroepiandrosterone constituted a major portion of the total 17-ketosteroids excreted.

In three patients who had become amenorrheic, menses resumed after treatment with o,p'DDD. This suggests that ovarian function is not diminished by the drug.

## DISCUSSION

These data provide evidence of limited therapeutic effect upon a relatively rare cancer. However, in relation to the field of cancer chemotherapy, these findings are especially significant because they provide an example of an agent that is able to exert its lytic effect almost entirely upon one tissue as well as upon a neoplasm arising from that tissue. Such specificity would appear to be especially valuable in drugs used in cancer chemotherapy.

These clinical experiences have impressed upon us the special difficulties involved in treatment of patients with large abdominal masses. Not only does infarction of the tumor mass contribute to the morbidity and mortality, but the effects of local pressure and infiltration of adjacent viscera may also prove to be irreversible. It would therefore seem to be indicated that all patients with adrenal carcinoma be carefully observed after surgery for the earliest evidence of recurrence, with special emphasis on the levels of steroid excretion; o,p'DDD could then be given when the steroid excretion first increases, even though palpable or visible metastases had not yet appeared.

In the case of patients in whom complete removal of adrenal cancer is not possible, it would seem desirable to prepare them for subsequent chemotherapy by the removal of as much of the tumor as is surgically feasible. Such an approach would probably increase the likelihood of successful chemotherapy.

Since the spontaneous clinical course of metastatic adrenal cancer may cover several years, remissions of a few months represent only limited effects upon length of survival. However, we are unaware of any reports of spontaneous remissions in this disease, so that the remissions noted are attributable to the chemotherapy.

It is likewise apparent that reduction in steroid production, per se, is not sufficient cause for such remissions, since treatment of a comparable group of patients with amphenone by us 15 resulted in a rapid decrease in steroid

excretion and no effect on tumor progression.

The data in figure 2 indicate that there is no necessary relationship between the total dose of o,p'DDD ingested and the response obtained. There was also no correlation between plasma levels of o,p'DDD and response. Thus, the factor of absorption of the drug was probably not the determinant of therapeutic response. It has so far not been possible to predict responsiveness to o,p'DDD, but in 15 of 17 cases in which the steroids were elevated there was an ultimate significant decrease in steroid production. These 18 patients thus reflect a wide spectrum of sensitivity to o,p'DDD, varying from the sensitive to the almost completely resistant cases.

The effects of o,p'DDD in man have reproduced all of the phenomena noted in the dog. However, man is apparently less sensitive to the drug. Acute suppression of the adrenal vein corticoids in the dog can be accomplished by 100 mg./Kg. of o,p'DDD orally for two days.<sup>17</sup> We have previously reported only partial suppression of urinary corticoid excretion in two eucorticoid women with breast cancer given 200 mg./Kg. for 14 and 19 days.<sup>10</sup> Their adrenal glands showed only minimal histologic changes. However, these differences are only quantitative, since sufficient o,p'DDD has resulted in unresponsiveness to ACTH, clinical manifestations of adrenal insufficiency, and destructive changes in the normal adrenal gland.

The initial studies with DDD in dogs suggested that the zona glomerulosa was resistant, but Tullner <sup>18</sup> has shown in the dog that a six-week course of o,p'DDD at a dose level of 50 mg./Kg. will result in necrosis of the entire adrenal cortex. The clinical counterpart of this phenomenon is the poor response to sodium restriction seen in two subjects after prolonged admin-

istration of o,p'DDD.

The gastrointestinal intolerance to o,p'DDD presents a barrier to adequate treatment of many patients. We have tried many methods of administration, but anorexia and nausea have always appeared. An intravenous preparation of o,p'DDD <sup>19</sup> was given a limited clinical trial. It, too, led

to nausea, and afforded no apparent therapeutic advantage.

The effects of o,p'DDD on the central nervous system have not been well studied experimentally. DDT has been shown to cause pathologic changes in the central nervous system, 19 but prolonged administration of DDD to dogs did not result in tremors or pathologic alterations in the brain. 1 It has been stated that DDD potentiates the action of barbiturates in the dog. We have been impressed by the drowsiness, lethargy and, rarely, severe somnolence that has occurred. This was particularly noticeable with the intra-

venous administration of the drug when the rate of administration was greater than from 2 to 4 gm. per 24 hours. This central nervous system depression proved to be reversible in each instance when the drug was discontinued.

It would appear that a beginning has been made toward the ultimate development of a highly specific oncolytic agent for the treatment of patients with inoperable or recurrent adrenal carcinoma. Further experimental and clinical study directed toward the elucidation of the mechanisms underlying the selective action of ortho, para prime DDD and toward the derivation of less toxic analogues of this agent is clearly indicated.

#### SUMMARY

Ortho, para prime DDD was given to 18 patients with metastatic adrenocortical carcinoma, resulting in objective regression of metastases in seven patients, significant steroid suppression in seven additional patients, and no apparent effect in four. The average course of treatment has consisted of from 8 to 10 gm. of o,p'DDD by mouth for from four to eight weeks.

There was no evidence of toxicity to liver, kidneys or bone marrow. All patients experienced significant anorexia and nausea, and some showed central nervous depression varying from mild lethargy to somnolence.

These toxic effects were reversible.

Evidence was obtained that high doses of o,p'DDD caused histologic damage and functional impairment of the normal adrenal gland.

#### SUMMARIO IN INTERLINGUA

Esseva administrate o,p'DDD a 18 patientes con metastatic carcinoma adrenocortical, con le resultato de un objective regression de metastases in septe patientes, de un significative suppression steroidic in septe alteres, e nulle apparente effecto in le remanente quatro. Al media, le curso therapeutic consisteva de 8 a 10 g del droga per die per via oral durante inter quatro e octo septimanas.

Esseva notate nulle toxicitate de hepate, ren, o medulla ossee. Omne le patientes experientiava grados significative de anorexia e nausea. Plures manifestava depression del systema nervose central, ab leve lethargia usque a somnolentia. Iste

effectos toxic esseva reversibile.

Esseva determinate que alte doses de o,p'DDD causa damnos histologic e vitiation functional in normal glandulas adrenal human.

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# MUSCULAR HYPERPLASIA OF THE LUNG: A PHYSIOPATHOLOGIC ANALYSIS \*

By Frank D. Gray, Jr., M.D., F.A.C.P., and Albert S. Field, Jr., M.D., New Haven, Connecticut

HYPERPLASIA of the smooth muscle in the lung has been known to occur under pathologic conditions since 1872. Orth <sup>16</sup> cites Rindfleisch, and von Stössel <sup>22</sup> refers to Buhl, <sup>6</sup> who used the term "muscular cirrhosis of the lung" for the condition. Arnold, <sup>1</sup> however, had noted muscular hyperplasia of the pleura in 1867, and referred to a thesis by Leo-Wolf <sup>13</sup> published in 1832. Rubenstein et al., <sup>19</sup> in reporting two cases, suggested "muscular hyperplasia" as the term which describes the pathology most

adequately.

Proliferation of smooth muscle has been described in "honeycomb" lungs, 12 in the walls of congenital cysts, 2 cystic transformation of the lung, 17 and in association with tuberous sclerosis. 3, 8, 14, 20 It may occur with cardiac disease, especially mitral stenosis and congestive failure. 11 In a pathologic study of 176 lungs, Harkavey 11 found it to be present in 13 cases of emphysema. Liebow et al. 15 collected 20 examples from 436 surgical lung specimens. Twelve of the 436 specimens showed emphysema, and five of the 20 examples occurred in these cases of emphysema. The remaining examples were seen in bronchiectasis, abscess, bronchitis, bronchiolitis, tuberculosis and tumor. The frequent association with inflammation led Rubenstein et al. 19 to consider this as the underlying stimulus for muscular hyperplasia, though they emphasized that smooth muscle lacks the capacity to regenerate following injury. Its increase may be a response to a need for increased functional capacity related to the degree and duration of pulmonary insufficiency.

The proliferated muscle is found in the walls of air passages, blood vessels and lymphatics, as well as in the connective tissue of the alveolar septa and the pleura. Bundles and sheets of smooth muscle narrow or even obliterate air passage-ways as well as blood vessels, and a polypoid mass of hyalinized muscle may obstruct a major bronchus; thus distention of pulmonary tissue and bullae formation occur. Liebow et al.<sup>15</sup> suggested that muscular hyperplasia may be the primary cause of emphysema in some cases, and the explanation for the improvement occasionally experienced following the use of antispasmodic drugs in these cases. As they indicated, the reason for the increase in smooth muscle of the lung is not clear, although entrap-

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ment of muscle under increased tension could be a cause of hypertrophy. Organizing pneumonitis and the development of a rich collateral blood supply, chiefly venous, might contribute to smooth muscle proliferation. The formation of bullae involves compaction of lung tissue, with remnants of bronchiolar walls and their associated blood vessels giving rise to masses of residual smooth muscle. A somewhat similar opinion was expressed by

Table 1
Clinical Characteristics of 17 Cases Reported in the Literature

	Rosendali7	Berg and Nordenskjöld <sup>3</sup>	Berg and Vejlens <sup>2</sup>	Dejerine and Sottas®	Rubenstein et al. <sup>19</sup> (2 cases)	Licht <sup>14</sup>	von Stössel¤ (2 cases)	Buchman <sup>5</sup> (2 cases)	Roubier et al.18	Bruce	Samuelsen <sup>20</sup>	Dawson <sup>6</sup>	Burrell and Ross?	Heppleston <sup>12</sup>	Noted	Denied	Not reported*
Age	51	33	32	53	63 65	63	51 43	84 51	76	29	49	31	36	39			
Sex	F	F	F	M	F	F	M F	M	M	F	F	F	F	F			
Dyspnea	1	1	1	1	2	1	2	1	_	0	1	1	1	1	14	1	2
Cough	_	-	0	1	2	1	2	1	-	1	1	1	-	-	10	1	6
Expectoration	-	-	0	1	2	1	2	1	-	1	1	1	-	-	10	1	6
Sputum:					4			1				1			3	0	
Nonpurulent Purulent				1	1		1	1		1		1			4	0	8
Hemoptysis	1			0	0		1	1		1	1	1			6	2	9
Fever	0	-	0	1	2	0	0	-	-	0	-				3	5	9
Cyanosis	-	1	1	-	1	1	2			0	_	1	1	_	8	1	8
Clubbing	_	_	-	-	1	_	_		_	0	_		_	-	1	1	15
Râles	1	0	0	1	2	1	2	1	-	1		0	-	-	9	3	5
Wheezing	0	0	0	1	_	-	1	_	-	-	-	0	-	-	2	4	11
Pleurisy or pleural				.												0	
effusion				1	1	1	1							1	5	0	12
Spontaneous pneumothorax		1	1				1					1		1	5	0	12
†Pulmonary		1	1											1	3	0	1.2
hypertension	0	1	_		1	1	'2				0	0	1	_	6	3	8
†Typical x-ray	1	1	1		2	i	2			1	1	1	_		11	0	6
Pathologic con-	1		1		-					-					-	-	
firmation	1	1	1	1	2	1	2	2	1	1	1	1	1	1	17	0	0

<sup>\*</sup> The absence of a specific sign or symptom cannot be assumed when not specifically mentioned. For this reason the tabulation of features not reported was included, as well as those noted and denied specifically.

† See text for description and criteria.

Heppleston.<sup>12</sup> He considered the muscular hyperplasia in tuberous sclerosis to be a part of the generalized disease process, and its occurrence in honeycomb lung a compensatory mechanism to encourage expulsion of air.

The clinical picture in 17 cases found in the literature is summarized in table 1. All of these had pathologic confirmation of the diagnosis by microscopic examination of tissue. In some there was an associated pathologic condition which contributed to the symptomatology, i.e., pneumonia

or pneumothorax. The symptoms occurring most frequently were dyspnea in 14 and cough in 10 cases. The sputum was purulent in four of the 10 patients who complained of cough. Six had a history of hemoptysis. Spontaneous pneumothorax was a significant complication in five. It occurred more than once and on both sides in some cases. Pleurisy was reported in five cases, with chylous pleural effusion or ascites in two. Fever was present in three. Of the physical signs, râles and cyanosis were most prominent, while pulmonary hypertension was suggested in six. Evidence for the latter was an accentuated pulmonic second sound, increase in the size of the hilar or pulmonary artery x-ray shadows, or right heart dilatation at post mortem. Polycythemia was reported once. One patient had had treatment for syphilis nine years before death; his serologic tests were negative shortly before death. Wheezing was noted twice. The age distribution at death was fairly even from 29 to 84 years. Curiously, all of the males were 51 years or over, and all of the females were 51 years or less, except for two, who were both 63. Chest x-rays were reported in 11 of the 17 cases. They were usually described as showing a netlike or a reticular pattern in the involved areas, caused by irregular flecks or small branching shadows surrounding translucent zones, varying from the size of a pinhead to many centimeters in diameter. These changes have suggested miliary tuberculosis, Boeck's sarcoid, silicosis, lymphangitic carcinomatosis, cystic lung disease and pulmonary congestion with induration secondary to cardiac failure.

In most instances the course of the disease was remarkable for the duration of symptoms. However, there were three who had no chronic respiratory symptoms before death. One of these was an 84 year old man dying of a cerebral vascular accident whose lungs showed muscular hyperplasia on post mortem; <sup>5</sup> the other two, 53 and 76 years old, died of pneumonia. <sup>9,18</sup> One of the 17 cases had dyspnea due to carcinoma of the trachea. <sup>5</sup> On the other hand, there were two with chronic cough and expectoration from childhood; <sup>4,22</sup> one of these had an initial, severe airway infection. The remaining cases had gradually increasing symptoms of respiratory insufficiency of weeks' to several years' duration. The course is usually insidious, interfering little with activity at first, and lasting many years from onset to death. The terminal stages of the illness are characterized by either pulmonary insufficiency or cardiac failure, or both.

The vital capacity was measured in three of the cases. It was 2.3 L. and 1.5 L. in two, and in the third was determined twice, 2.8 L. and 1.5 L. As far as can be determined, no other cases have been reported with pulmonary function studies, nor have more complete studies been done, although Storstein has discussed the physiologic aspect briefly.<sup>21</sup>

This paucity of physiologic studies led our laboratory to perform an extensive battery of cardiopulmonary function tests on all patients suspected of having this disease. Of those so studied, pathologic confirmation of the

diagnosis has been obtained in five cases thus far. The feeling that these data should contribute to a better understanding of a process probably less rare than is generally supposed has engendered the present communication.

# CASE REPORTS

Case 1. A 52 year old white male was admitted in October, 1957, because of increasingly productive cough and exertional dyspnea. The cough had begun five years previously, and had increased until, on admission, he was raising one-half cup of white sputum daily. He had noticed that the cough was worse upon lying down, particularly on the left side. His dyspnea was noticeable when climbing one flight of stairs, and he frequently had audible wheezing. During the period of his symptoms he had lost 12 pounds in weight, but his appetite had remained good. At least 15 years earlier, and before the onset of other symptoms, he had noted the development of finger clubbing.

The past history and system review were otherwise noncontributory, except that the patient is known to have had a positive tuberculin test with negative histoplasmin

TABLE 2 Clinical Data in Five Cases

	Dura-			D	yspnea		Club	bing	Clinical Evidence	Clinical o
Case	tion of Cough, Years	Sputum*	Hemop- tysis	Dura- tion, years	Degree†	Cyanosis	Present	Dura- tion, years	of Con- gestive Heart Failure	Autopsy Evidence of Cor Pulmonale
1 2	5 11	+++	0 Yes	5	+++++	Slight	Yes 0	15	0	0 Yes
3 4	15	++++	Yes Yes	15‡	++++	Yes	Ves Ves	6	Yes Yes	Ves 1

\* = Amount of sputum graded as follows: +, scant; ++, 1 or 2 tablespoonfuls; +++,

½ cup; ++++, over ½ cup daily.

† = Degree of dyspnea graded as follows: +, over 1 flight of stairs; ++, 1 flight of stairs; +++, level walking; ++++, at rest.

‡ = Recurrent episodes of "asthma" for 46 years.

and coccidioidin tests. The only significant information in his family history is that his mother had died of diabetes mellitus. His occupational history may be significant in that he was a printer exposed to paraffin spray as well as to gold and bronze dusts. He smoked about one package of cigarettes daily.

On physical examination the blood pressure was 115/90 mm. of Hg; pulse rate, 108; respiratory rate, 16; temperature, 100° F. The patient appeared to be slightly cyanotic. The head, eyes, ears, nose, throat and neck were unremarkable. Breath sounds were distant over the apices, bronchovesicular elsewhere. Expiration was prolonged, and there were fine moist râles throughout. The heart was unremarkable. The abdomen was scaphoid, and the liver edge was felt 2 cm. below the costal margin. There was advanced finger clubbing, but no edema of the extremities.

Laboratory data revealed: hemoglobin, 12 gm.; hematocrit, 40%; white cell count, 10,650, with 74% polymorphonuclears, 23% lymphocytes, 2% monocytes and 1% basophils. The urine was completely negative. Serum albumin, 2.87 gm.%; globulin, 4.09 gm.%. The gamma fraction was elevated on electrophoresis. Serum calcium, 10.7 mg.%; inorganic phosphorus, 3.6 mg.%. A battery of liver function

Physiologic Data in Five Cases (Symbols as noted in Federation Proc. 9; 602, 1950.) TABLE 3

Vr. Vr. CO.	min.	0.560	0.653 12	0.653 12 0.829 17	0.653 12 0.829 17 0.684 13 0.508 11	0.653 12 0.829 17 0.684 13 0.508 11	0.653 0.829 0.684 0.508 0.600
%	Rest With On	100					
idal,	7 Min. R	0	0	2.7			
End-tidal, N2%	4 Min.	9.0	1.8	8: 1	1.8	1.8	9.2
MBC. liters	min.	108	114	114	114 70 88 38	114 70 88 38 32	114 70 38 38 38 38 32
RV/TLC		0.24	0.22	0.22	0.22	0.22 0.39 0.42 0.47	0.22 0.39 0.42 0.47 0.72
TLC,	liters	4.559	4.446	4.446	6.358 6.671 4.424	6.358 6.671 4.424 6.395	6.358 6.671 4.424 6.395 7.261
RV.	nters	1.097	0.994	2.492	2.492 2.784 2.082	2.492 2.784 2.082 4.612	2.492 2.784 2.082 4.612 5.520
FRC.	liters	3.160	2.870	2.870	2.870 4.150 4.380 2.880	2.870 4.150 4.380 2.880 5.110	2.870 4.150 2.880 5.110 6.100
IC,	liters	1.399	1.576	2.208	2.208 2.291 1.543	2.208 2.291 1.543 1.285	2.208 2.291 1.543 1.285
ERV,	nters	2.063	1.876	1.658	1.876 1.658 1.596 0.799	1.876 1.658 1.596 0.799 0.498	1.876 1.658 1.596 0.799 0.498
VC,	nrers	3.462	3.452	3.452	3.452 3.866 3.887 2.342	3.452 3.866 3.887 2.342 1.783	3.452 3.866 3.887 2.342 1.783
Case		1 A	В	B 2 A	B B C C	2 A C C S	2 A B C C B A

A = Base line study.
B = After inhaling an aerosol of Vaponefrin.
C = 24 years after A. = Fell to 86% after 1-minute standard exercise.

+ = Fell to 85% after 1-minute standard exercise.

tests was within normal limits except for a bromsulfalein retention of 13.6%. The histoplasmin skin test was positive; the coccidioidin test, negative. The chest x-ray showed a dense, diffuse, honeycombing density with areas of radiolucency in the apical regions suggesting bullae, particularly on the left. The electrocardiogram showed only borderline elevation of ST in Leads 1, 2, AVF, V5 and V6. There was no evidence of right ventricular hypertrophy. Cardiopulmonary function tests are recorded in tables 3 and 4.

The apical segment of the left upper lobe was resected, and pathologic examination revealed a large bulla lined by cuboidal epithelium and surrounded by dense fibrous tissue with foci of calcification and collections of lymphocytes. The parenchyma revealed extensive smooth muscle proliferation with fibrosis and a heavy infiltration of inflammatory cells. The respiratory epithelium had proliferated into the terminal air passages. There were a proteinaceous material in the distal air passages and collections of fine, pigmented granules embedded in the scar tissue. Following resection, improvement was noted in all symptoms.

Final diagnosis: chronic bronchitis, bronchiolitis, interstitial fibrosis, pulmonary proliferation of smooth muscle tissue, and bullous emphysema.

Case 2. A 39 year old Negro male was seen in our clinic in March, 1957, with the story that, 11 years before, he had developed acute bronchitis and pneumonia.

Table 4
Special Physiologic Studies in Two Cases
(Symbols as noted in Federation Proc. 9: 602, 1950.)

Case	Oz Used, ml./LV	Prod., ml./LV	RQ	Saon %	End- tidal, CO <sub>2</sub> %	Ů./min.	VD, liters	A-a, mm. Hg	Pa <sub>CO2</sub> , mm. Hg	Status
1	28.4	24.2	0.85	91	4.45 1.95	3.39	0.278	<u>26</u>	45.9	Rest Hyper- ventilation
	29.8	24.6	0.82	86 91	3.7 4.4	=	_	_	=	Exercise Recovery
2	_			90	_	2.17	0.128	49	36	Rest

Subsequently he had had 23 hospital admissions for exacerbations of his bronchitis and for recurrent pneumonia. In the interim he had had a persistent, chronic cough, productive of scant sputum, with almost continuous wheezing. During acute episodes he had hemoptysis, a foul, greenish yellow sputum, and fever, with chest pain in various locations.

The patient's past history is contributory only in that he had had gonorrhea in 1936, with no known complications or sequelae. Serologic tests for syphilis have always been negative. There is no record of a Frei test.

No data are available about the patient's family history. His personal history indicated that he consumed large amounts of alcoholic beverages and smoked about one package of cigarettes daily. He had worked as a laborer in various jobs. There was no known exposure to irritant dusts in his work.

On physical examination, the blood pressure was 120/70 mm. of Hg. There was no clubbing or edema. At times, cyanosis had been noted during acute episodes. The patient's teeth were in very poor condition. There was a prolonged expiratory wheeze, with harsh rhonchi and scattered areas of very fine, crackling râles throughout all lung fields. The heart did not appear to be enlarged. The rhythm was regular; there were no murmurs. The pulmonic second sound was greater than the

aortic second sound. No organs, masses or tenderness were found in the abdomen. The extremities were not unusual. There was no edema. The neurologic examination was grossly within normal limits.

Laboratory data revealed: hematocrit, 50%; white blood cell count, 7,000, with a normal differential. Subsequently, the eosinophil count reached as high as 14%. The urine was within normal limits. Serum albumin, 3.16 gm.%; globulin, 4.67 gm.%, with an elevation in the gamma fraction on electrophoresis. Serum sodium, 137.5 mEq./L.; chloride, 100.2; CO<sub>2</sub>, 24.6; potassium, 4.9; serum nonprotein nitrogen, 25 to 30 mg.%. Sputum culture revealed chiefly *Hemophilus influenzae* and Pneumococcus. At times there was heavy growth of Proteus. No acid-fast bacilli were seen. Cardiopulmonary function tests are reported in tables 3 and 4.

The PPD skin test was positive. The electrocardiogram revealed right axis deviation, with a high, prominent R in aVR, and "P" pulmonale. The chest x-ray revealed low, flat diaphragms, with massive areas of density alternating with radio-lucent areas, suggesting interstitial fibrosis and bullous emphysema. Bronchograms revealed no bronchiectasis, but there was failure of filling of the left lower lobe, pectoral segment of the left upper lobe, and right middle lobe bronchi. The patient was referred to Woodruff Hospital (a chronic disease and rehabilitation hospital), where he was treated vigorously with postural drainage, breathing exercises and inhalation therapy. Following this, he did very well until April, 1958, when he was admitted because of spontaneous pneumothorax. Thoracotomy revealed that a large left upper-lobe bulla had ruptured, and a resection was carried out, following which the patient made an uneventful recovery. He has subsequently done well, except that a large bulla has appeared in the right upper lobe. However, there have been no complications.

Pathologic report of the excised specimen revealed the presence of emphysema with bullae, peribronchial inflammation and fibrosis, interstitial fibrosis, and extensive hyperplasia of smooth muscle tissue. The latter appeared in dense masses, strands and sheets in the wall of the excised bulla and in the peribronchial and interstitial areas.

Final diagnosis: chronic bronchitis, bullous emphysema, interstitial fibrosis, and pulmonary proliferation of smooth muscle tissue.

Case 3. A 49 year old white male was admitted in May, 1956, because of an exacerbation of asthma, which had been recurrent since the age of three years. Most of his trouble occurred in damp weather and during the winter months. During the preceding 10 to 15 years he had had constant wheezing and shortness of breath on mild exertion. His cough had become progressively worse over the years, and at the time of admission he was raising one cup of green sputum daily. The cough was equally bothersome day or night. In the past he had noted blood-streaking of his sputum. Although there had been no ankle edema, during the preceding year he had complained of orthopnea.

The patient's past history and system review reveal an episode of pneumonia in 1947, a long history of hay fever in childhood, and a long history of chronic alcoholism. The family history revealed that his mother was living and well, his father had died of carcinoma of the stomach, and four siblings were living and well. He had smoked from one to one and a half packs of cigarettes daily throughout most of his adult life.

On physical examination the patient's blood pressure was 110/84 mm. of Hg; pulse rate, 120; respiratory rate, 20. The head and neck were not unusual, except for distention of the neck veins in the sitting position. Chest expansion was diminished, and the patient used accessory muscles for breathing. Intercostal retraction was noticeable. The lungs were hyperresonant, with diffuse expiratory wheezes throughout and fine, moist, basilar râles. The heart was rapid but not otherwise

unusual. No organs, masses or tenderness were palpated in the abdomen. There was no cyanosis, clubbing or edema.

Laboratory examination revealed: hemoglobin, 15.5 gm.; hematocrit, 45 to 50%; white cell count, 16,000, with 84% polymorphonuclears, 11% lymphocytes and 5% monocytes. The urine was completely normal. Blood nonprotein nitrogen, 29 mg.%; albumin, 3.78 gm.%; globulin, 3.17 gm.%; serum carbon dioxide, 29.3 mEq./ L.; chloride, 94 mEq./L. The venous pressure was 110 mm. of water; circulation time (Decholin), 17 seconds. Cultures of the sputum, nose and throat revealed normal flora. The sputum was negative for acid-fast bacilli. The first-strength PPD skin test was positive. The chest x-ray showed diffuse interstitial infiltration with giant bullae, especially in the right upper lobe. The electrocardiogram revealed low voltage and delayed transition in the precordial leads. Cardiopulmonary function tests are recorded in table 3.

A segmental resection of the major right upper lobe bulla was carried out. The pathologic examination of the specimen revealed bullous emphysema, alveolar walls thickened by the presence of large masses of smooth muscle, and diffuse inflammatory changes of bronchi and bronchioles. Following resection, the patient had slight improvement in all of his symptoms.

Final diagnosis: chronic bronchitis, bullous emphysema, and pulmonary proliferation of smooth muscle tissue.

Case 4. A 50 year old white man entered the hospital for the last time in July, 1958. He stated then that since 1952 he had had increasing exertional dyspnea, cough productive of about two ounces of white, blood-streaked sputum daily, and occasional ankle swelling. He had frequent exacerbations with loud wheezing. All of these symptoms were mild in the beginning, but became so severe that by 1955 he was totally disabled. It is of interest that in 1952, when his symptoms were minimal, pronounced finger clubbing was noted. His history also included repeated epistaxis.

The patient's past history and system review reveal only a tonsillectomy at the age of 33, and a hernia repair at the age of 48. His personal history indicates that he worked in a brass factory, but had had no known exposure to silica or other irritating dusts. He smoked about one package of cigarettes daily.

On physical examination the patient's blood pressure was 130/70 mm. of Hg; pulse rate, 120; respiratory rate, 26; temperature, 97.8° F. He was obese and very cyanotic, with an advanced degree of finger clubbing. The head, eyes, ears, nose, throat and neck were not remarkable. The chest moved symmetrically, but with intercostal retraction and a prolonged expiratory phase. There were fine moist râles and expiratory wheezes throughout all lung fields. The heart sounds were distant but otherwise not unusual, except for the tachycardia. No organs or masses were felt in the abdomen, and there was no peripheral edema.

Laboratory examination revealed a hematocrit of 74%, which dropped to 50% after phlebotomy. The white cell count was 12,700, with 75% polymorphonuclears, 20% lymphocytes, 3% monocytes and 2% basophils. The urine was entirely normal. Chest x-ray revealed diffuse interstitial densities with some areas of rarefaction, suggesting small bullae. Cardiopulmonary function tests are recorded in table 3.

The patient was placed on a reducing diet, on which he lost 25 pounds. In addition, he was given bronchodilators, positive pressure breathing, postural drainage, and diaphragmatic breathing exercises. On this regimen he improved considerably until three weeks before death, when he became febrile, and over the next three weeks rapidly developed more cough and dyspnea. In spite of antibiotics and oxygen, he continued to grow worse and died. An autopsy was performed which was remarkable chiefly for the heart and lungs, the former showing

right ventricular hypertrophy and the latter dense interstitial fibrosis with extensive smooth muscle proliferation, bronchitis, bronchiolitis, multiple small areas of pulmonary emboli with infarction, and small bullae.

Case 5. A 69 year old Italian-born male was admitted in February, 1955, complaining of cough, weakness, and shortness of breath. He had first visited the hospital 30 years previously, when he was found to have secondary syphilis with positive serologic tests and skin lesions. He was next seen a year later because of a stab wound in the back. At that time the entire pleura appeared by x-ray to be thickened. He was given several courses of treatment for his syphilis, and was then seen in our hospital in 1949 because of a 17 pound weight loss, dry cough and dyspnea. Chest x-ray revealed linear infiltrations in the lower half of the right chest, and a honeycomb appearance of both lung fields, with a shift of the heart and trachea to the left.

The patient was not seen here again until 1955, when he came in emaciated, very weak, coughing constantly, and expectorating large amounts of purulent sputum with blood-streaking. At this time he was quite cyanotic and very short of breath, even at rest, but had no orthopnea. Periodically he developed loud wheezing.

The past history and system review were otherwise unremarkable, except for diminished hearing and the development of hoarseness over the preceding three months. The family history was unremarkable. The patient's personal history revealed that he had worked as a gun etcher for many years, and smoked 10 to 15 cigars a day.

On examination the blood pressure was 125/85 mm. of Hg; pulse rate, 120; respiratory rate, 36; temperature, 101.6° F. There were early cataracts in both eyes, with narrowing of the retinal arterioles and AV nicking. There were scattered white fluffy exudates in both fundi. The patient had wheezes, râles and rhonchi bilaterally, the fine râles suggesting the crinkling of tissue paper. There were dullness and bronchial breathing over the right lower lobe. The heart sounds were of poor quality, with an accentuated pulmonic second sound. There were many extra beats, and a precordial systolic murmur with an intermittent diastolic gallop along the left sternal border. No organs or masses could be felt in the abdomen. There was moderate clubbing with cyanosis, but no edema.

Laboratory examination revealed: hemoglobin, 14 gm.; white cell count, 20,000, with 86% polymorphonuclears, 7% lymphocytes and 7% monocytes. The urine showed only occasional granular casts. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was "nonreactive." Blood nonprotein nitrogen 48 mg.%; albumin, 2.18 gm.%; globulin, 6.31 gm.%. Serum CO<sub>2</sub>, 31.7 mEq./L.; chloride, 81.5; sodium, 131.3; potassium, 4.5. A battery of liver function tests showed, as the only abnormality, a 2 plus cephalin flocculation at 24 and 48 hours. Sputum was negative for acid-fast bacilli. The first-strength PPD skin test was negative, but second-strength was positive. Venous pressure was 85 mm, of water; circulation time (Decholin), 30 seconds. A bone marrow aspiration was normal. A liver needle biopsy showed only fine vacuolization of cells, probably due to antibiotics, as well as hyperplasia of the reticuloendothelial cells. The electrocardiogram showed a tachycardia and moderate left axis shift. AVR suggested right ventricular hypertrophy. Chest x-ray (figure 1) showed diffuse interstitial infiltration, with many small and large bullae, cardiac enlargement with fullness of the conus, and pulmonary artery shadows. Cardiopulmonary function tests are recorded in table 3.

The patient died on a subsequent admission and an autopsy was performed. The autopsy revealed hypertrophy of the right ventricle, extensive inflammatory reaction of the bronchi and bronchioles, with interstitial proliferation of fibrous tissue, bullous

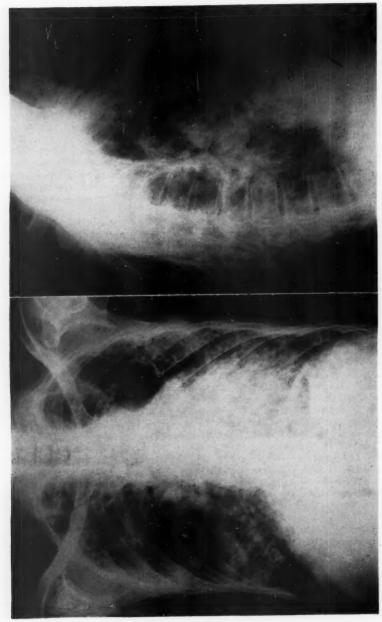


Fig. 1. Case 5. Chest x-ray.

emphysema, pneumonia of the right lower lobe, and massive infiltration of the lung parenchyma by sheets of smooth muscle tissue. A subsidiary diagnosis was fusion of the two kidneys.

Final diagnosis: chronic bronchitis, bullous emphysema, interstitial fibrosis, and pulmonary proliferation of smooth muscle tissue. The precipitating cause of death was felt to be lobar pneumonia of the right lower lobe. Clinically, the patient had cor pulmonale and a history of syphilis.

# DISCUSSION

At the time our patients were examined, they had shown evidence of pulmonary disease for from six to 15 years. Interestingly, the two who were least incapacitated (cases 1 and 3) had the longest history, if one considers the 15-year history of clubbing in case 1. These vagaries are consistent with the reports of earlier observers.<sup>4, 5, 22</sup>

The clinical picture (table 2) is one of progressive cough productive of blood-streaked sputum, and exertional dyspnea associated with signs which included fine râles, wheezes, cyanosis and finger clubbing, although these signs are not invariable. In some cases the disease tends to be localized with less severe disability, in others generalized with great disability. In case 3 the disease was localized to the apical regions and at least some of the dyspnea can probably be ascribed to left heart failure, since he had clearcut orthopnea. However, left heart failure itself may be the result of chronic pulmonary disease.<sup>10</sup> As the disease progresses, cor pulmonale becomes a prominent feature.

The copious character of the sputum suggests that chronic infection played an important part in our cases, although many of the previously reported cases did not show this (table 2). One of our patients (case 2) had been admitted 23 times for pneumonia when we saw him. The fine character of the widespread rales suggests that small bronchi and bronchioles are involved, and this is borne out by the pathologic examination.

In all but one patient (case 1), the physiologic studies (table 3) show severe restriction reflected in the low inspiratory capacity, and distention reflected in the high functional residual capacity and high ratio of residual volume to total lung capacity. The index of intrapulmonary gas distribution (end-tidal nitrogen) was abnormal in three, normal in two. It is of interest that in case 1 the four-minute intrapulmonary mixing index was worse after breathing Vaponefrin than before. This suggests that nonventilated lung areas were converted to poorly ventilated areas by the bronchodilator. The decrease in the degree of distention, as shown by the drop in functional residual capacity after Vaponefrin inhalation in this patient, suggests either a bronchospastic element or mucosal edema. Either could have been influenced by the epinephrine-like action of the drug. In contrast, the other patient who was studied before and after Vaponefrin (case 2) demonstrated an increase in functional residual capacity.

The arterial oxygen saturation was low in four of the five patients, and

some evidence of carbon dioxide retention was found in two. Curiously, case 3, who had a venous serum carbon dioxide content of 29.3 mM/L. (above our upper limits of normal), had a high resting arterial oxygen saturation. The carbon dioxide retention may have been related to a low alveolar ventilation, or to the poor intrapulmonary gas distribution.

Additional physiologic studies were done on cases 1 and 2 (table 4). In case 1 they revealed an inability significantly to increase oxygen or carbon dioxide exchange per liter of ventilation during exercise, a fall in arterial oxygen saturation with exercise, and a fall in end tidal carbon dioxide with exercise. These findings suggest that perfusion could not keep pace with total ventilation during exercise, or that dead space ventilation increased disproportionately. Alveolar ventilation was mildly depressed and dead space volume increased. There was an unusually high alveolar-arterial oxygen pressure gradient with normal arterial carbon dioxide tension. The increased gradient was not due to a venous shunt, since the arterial blood oxygen saturation promptly rose to 100% upon the patient's breathing pure oxygen; hence, it must have been due to alveolar-capillary block. The high A-a gradient in case 2 was related in part to venous admixture, but probably largely to alveolar-capillary block.

The pathogenesis of this disease remains uncertain, although cogent speculations have been raised. 12, 15, 19 Considering the clinical, physiologic and pathologic features, one is tempted to propose a hypothesis of chronic inflammatory disease of the small bronchi and bronchioles which produces obstruction with emphysema and bullae formation, and stimulates the rampant hyperplasia and dissemination of smooth muscle tissue. The latter, together with interstitial fibrosis, produces severe restriction and block of gas exchange across the alveolar-capillary membrane, as well as obstruction to the vascular bed. Compaction of remnants of smooth muscle in the dense tissue surrounding the bullae enhances the picture. More studies, particularly in the incipient stages, are needed to test the accuracy of such

a concept.

This picture is difficult to distinguish clinically from diffuse bronchiolectasis and interstitial fibrosis, but a clinical history of cough with blood-streaking, episodes of asthmatic wheezing, cyanosis, finger clubbing and eventual cor pulmonale, with physical signs notable for the widespread presence of fine, tissue paper-like râles, should suggest the diagnosis, if the x-ray appearance (figure 1) is one of diffuse interstitial infiltration with many bullae of variable size. At present, little is known about specific treatment. From our experience it is difficult to assess the long-term value of excising the larger bullae which may appear in the lung apices. Antibiotics should be used to combat infection. The regimen so frequently used in chronic pulmonary disease, which involves cessation of smoking, postural drainage, inspiratory positive pressure breathing, bronchodilators, expectorants and breathing exercises, will probably prolong useful life.

## SUMMARY

1. The literature describing muscular hyperplasia of the lung is briefly reviewed, and five new cases are reported with pathologic confirmation and extensive physiologic studies.

2. Widespread hyperplasia of pulmonary smooth muscle appears to be associated with chronic inflammation. It leads to bronchial and bronchiolar obstruction, bullous emphysema, and infiltration of the alveolar wall. Some of the apparent hyperplasia may represent smooth muscle remnants in areas of destroyed lung.

3. The clinical picture is one of long-standing chronic cough, purulent sputum, dyspnea, cyanosis, and often finger clubbing, with diffuse wheezes and fine râles throughout the lung fields.

4. Physiologically the difficulties consist of airway obstruction, impaired intrapulmonary gas distribution, and alveolar-capillary block. The process leads slowly but inexorably to cor pulmonale.

### SUMMARIO IN INTERLINGUA

Ben que reportos de extreme hyperplasia del tissu de musculo lisie in le pulmon se trova in le litteratura medical depost 1832, solmente 17 casos ha essite reportate con detalios clinic sufficiente pro le establimento de un entitate specific. Pro iste 17 casos nulle studio physiologic esseva reportate. Cinque nove casos es presentate con studios physiologic del function cardiopulmonar,

Extense hyperplasia del lisie musculo pulmonar ha essite associate con numerose conditiones pathologic, sed in quasi omne le casos un inflammation chronic esseva presente. Hyperplasia de musculo lisie resulta in obstruction bronchial e bronchiolar, emphysema bullose, e infiltration del tissu interstitial alveolar. Residuos de musculo lisie in areas ubi le pulmon es destruite explica un certe parte del apparente hyperplasia, sed in casos nette, le quantitate de musculo incontrate es multo plus grande que lo que pote esser attribuite a iste processo. Le stimulo evocante le hyperplasia non es cognoscite, sed multe observatores crede que inflammation es le factor responsabile.

Iste patientes reporta un anamnese de tusse chronic, sputo purulente, hemoptysis, dyspnea, cyanose, e—frequentemente—digitos hippocratic. Exacerbationes es frequente e associate con facilemente audibile rhonchos. Le examine physic revela diffuse rhonchos in omne partes del campo pulmonar. Tests physiologic del function cardiopulmonar demonstra obstruction del vias aeree, un vitiate distribution intrapulmonar de gas, e bloco alveolo-capillar.

Finalmente le patientes manifesta signos de corde pulmonal e de disfallimento. Le tractamento consiste in combatter infectiones per antibioticos e in mantener libere passages respiratori de aere per medio de aerosoles bronchodilatatori e respiration a inhalation sub pression positive. Quando disfallimento cardiac se declara, digitalis e diureticos debe esser administrate.

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# CHARACTERISTICS OF SMOKERS COMPARED WITH NONSMOKERS IN A POPULATION OF HEALTHY YOUNG ADULTS, INCLUDING OBSERVATIONS ON FAMILY HISTORY. BLOOD PRESSURE, HEART RATE, BODY WEIGHT, CHOLESTEROL AND CERTAIN PSYCHOLOGIC TRAITS \* † ‡

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WHETHER the habit of smoking tobacco is related to the development of hypertension or coronary heart disease has long been a subject for discussion. Recently, this controversy has come into sharper focus as the result of statistical studies of death rates in relationship to the smoking habits of large population groups in the United States and Great Britain.1,2 The finding that smokers, especially heavy smokers, have a higher mortality rate from coronary heart disease than do nonsmokers makes it important to determine whether those who smoke are fundamentally different from those who do not, or whether smokers and nonsmokers are essentially alike. If alike, then smokers and nonsmokers may be considered as a single population with a uniform life expectancy. If, however, smokers have constitutional differences from nonsmokers, the two groups might have inherently different mortality rates, and one group could not serve as a control for the other in statistical studies.

To throw light on this problem, we have studied the smoking habits of 10 successive classes of Johns Hopkins medical students in detail, and have looked for associations between the smoking habits of each individual and certain genetic, physiologic, metabolic and psychologic characteristics. The extensive data obtained in a long-term study of the precursors of hypertension and coronary heart disease have been used for this purpose. Only a portion of the collected information has as yet been analyzed. Some of the salient findings which have appeared in our preliminary tabulations are here presented.

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# Метнор

The subjects were all Johns Hopkins medical students in good health and free from clinical evidence of hypertension and coronary heart disease. As part of the long-term study mentioned above, they were observed from many aspects while in medical school. These studies included detailed information about family history, a habit survey, measurements of blood pressure, heart rate, height, weight and cholesterol level, a cold pressor test, a double Master exercise test, a ballistocardiographic smoking test, and a Rorschach test.<sup>3-12</sup>

A total of 787 students was registered in the medical school in the classes of 1948 through 1957. Of these, 749 volunteered to be subjects in the long-term study, 15 refused to participate, and 23 were never asked, either

Table 1
Subjects Classified by Smoking Habits

Category	Type of Smoker	Ŋ	Men	. W	omen	T	otal
Category	Type or Emonet		%	N	%	N	%
0	Nonsmokers	194	27.4	27	33.8	221	28.1
1	Occasional smokers Regular smokers Cigarette smokers	75	10.6	7	8.8	82	10.4
2	Light (1-10/day)	52	7.4	12	15.0	64	8.1
2 3 4 5 6 7	Moderate (11–19/day)	49	6.9	4	5.0	53	6.7
4	Heavy (20 or more/day)	119	16.8	10	12.5	129	16.4
5	Pipe smokers	22	3.1	0	0.0	22	2.8
6	Cigar smokers	1	0.1	0	0.0	1	0.1
7	Pipe and cigar smokers	2 52	0.3	0	0.0	2	0.3
8	Mixed smokers (cigarettes combined with pipes and/or cigars)	52	7.4	0	0.0	52	6.6
9	Former smokers	31	4.4	0	0.0	31	3.9
X	Unknown smoking habits	110	15.6	20	25.0	130	16.5
Total		707	100.0	80	100.1	787	99.9
Total wi	th known smoking habits	597	84.4	60	75.0	657	83.5

because they left medical school within two weeks of admission or because they transferred into the third year class from other medical schools at times when it was not possible to study them. The smoking habit questionnaire was answered by 657 subjects, or 83.5% of the entire group (table 1). Information was not obtained on 92 of the subjects who coöperated in the general study, for several reasons, including the inauguration of the habit survey late in the academic course (class of 1948), changing methods of administration (especially class of 1952) and varying degrees of academic and economic pressure among the students; a few students left medical school before the habit survey was given out to their particular class. It is thought that the loss of information on this relatively small proportion of subjects introduces no serious bias.

Detailed information concerning smoking habits, then, was obtained from 657 subjects, of whom 597 were men and 60 were women. The smoking habits of this population are shown in table 1 according to the categories used in the habit survey questionnaire. In many of the subsequent tables these categories are pooled in various ways. Whenever this occurs, a footnote to the table in question indicates exactly which smoking habit categories are included in a given grouping. In particular, we have made use of the following groupings, and have referred to them in the text by the terms indicated below:

- "Nonsmoker," meaning not a regular smoker, includes categories 0 and 1.
- 2. "Regular smoker" includes all categories except 0, 1, 9 and X.
- 3. "Other regular smokers," when contrasted with heavy smokers, includes categories 2, 3, 5, 6, 7 and 8.

The former smokers were never grouped with either the smokers or the nonsmokers. Because of their small number, former smokers were usually omitted from the statistical analyses. Those with unknown smoking habits are not included in any of the subsequent tables or discussions.

In the statistical analyses, all subjects with known smoking habits who were studied for a given variable are included. Not every subject with known smoking habits completed all portions of the study. In general, a high proportion of them did. Where the total number of subjects is unusually low for a given variable (e.g., ballistocardiographic smoking test, cholesterol level), it is because that test was introduced at some time after the inception of the study. There are also minor variations in the numbers, particularly to be noted in table 6, because for technical or special reasons not every part of every test could be carried out.

#### RESULTS

The smoking habits of 657 Johns Hopkins medical students are summarized in tables 1 and 2. Table 2 shows that the population as a whole is quite evenly distributed between regular smokers and nonsmokers (49.2% versus 46.1%). When the smoking habits of successive classes of students are examined, however, a definite change in the proportion of regular smokers to nonsmokers is found with the passage of years. In the early classes, regular smokers, representing around 56% of the students, predominated, while at the end of the 10-year span the number had fallen toward 40%. The nonsmokers showed a gradient in the opposite direction, as did the percentage of subjects who had given up smoking entirely.

The smokers and nonsmokers were similar in regard to age. The age distributions for nonsmokers, heavy cigarette smokers and other regular smokers are shown in table 3; they were not significantly different when compared by the chi-square test. The proportion of nonsmokers, heavy

TABLE 2 Summary of Smoking Habits in Successive Classes of Johns Hopkins Medical Students

Class	Total Subjects	Subjects with Known	Regular	Smokers	Nons	mokers	Former	Smokers
	in Class	Smoking Habits	N	%	N	%	N	%
1948	79	50	28	56.0	20	40.0	2	4.0
1949	73	71	41	57.7	29	40.8	1	1.4
1950	73	68	38	55.9	27	39.7	3	4.4
1951	81	72	31	43.1	39	54.2	2	2.8
1952	86	60	34	56.7	25	41.7	1	1.7
1953	76	69	34	49.3	30	43.5	5	7.2
1954	84	62	29	46.8	28	45.2	5	8.1
1955	84	70	34	48.6	33	47.1	3	4.3
1956	77	66	29	43.9	33	50.0	4	6.1
1957	74	69	25	36.2	39	56.5	5	7.2
1948-1957	787	657	323	49.2	303	46.1	31	4.7

Regular smokers = categories 2, 3, 4, 5, 6, 7 and 8, table 1. Nonsmokers = categories 0 and 1, table 1.

% = percentage of subjects with known smoking habits.

cigarette smokers and other regular smokers in each age group was found to be rather constant: about 20% were heavy cigarette smokers, while 30% were regular smokers of some other kind.

A. Familial Occurrence of Hypertension and/or Coronary Heart Disease: The prevalence of hypertension and of coronary heart disease was higher among the parents of students who were regular smokers than among the parents of nonsmokers, as has been previously reported by us.13 The difference was significant when subjects with definite or questionable

TABLE 3 Distribution of Age at Graduation by Smoking Habits

Age at Graduation	Nons	mokers		Cigarette okers		Regular okers	T	otal
	N	%	N	%	N	%	N	%
23 or under	37	12.2	16	12.4	24	12.4	77	12.3
24-26	179	59.1	71	55.0	110	56.7	360	57.5
27-29	56	18.5	26	20.2	38	19.6	120	19.2
30-32	19	6.3	11	8.5	14	7.2	44	7.0
33 or over	12	4.0	5	3.9	8	4.1	25	4.0
Total	303	100.1	129	100.0	194	100.0	626	100.0

 $X_{s^2} = 1.152 \text{ P} > .99.$ 

Nonsmokers = categories 0 and 1, table 1.

Other regular smokers = categories 2, 3, 5, 6, 7 and 8, table 1.

TABLE 4 Prevalence of Hypertension among the Parents of Smokers Compared with Nonsmokers

Parental Hypertension	Nons	mokers	Sm	okers	Te	otal
ratental Hypertension	N	%	N	%	N	%
Present or question- able in one or both parents	80	29.0	113	38.3	193	33.8
Absent in both parents	196	71.0	182	61.7	378	66.2
Total	276	100.0	295	100.0	571	100.0

 $X_1^2 = 5.54 P = 0.02.$ 

Nonsmokers = categories 0 and 1, table 1. Smokers = categories 2 through 8, table 1.

parental hypertension were compared with subjects whose parents were free from that disorder (p = .02) (table 4). There was also a greater prevalence of parental coronary disease among students who were smokers than among those who were nonsmokers, but this trend only approached statistical significance (0.10 > p > 0.05). When subjects with definite or possible parental hypertension and/or coronary disease were compared with subjects whose parents were both free from these disorders, there were more smokers than expected with a history of parental cardiovascular disorders, and more nonsmokers than expected whose parents were both free from hypertension and from coronary disease (p = .02) (table 5).

B. Relationship of Blood Pressure and Heart Rate, at Rest and under Several Forms of Stress, to Smoking Habits: The circulatory characteristics of smokers and nonsmokers were appraised by observing the systolic pressure, diastolic pressure, pulse pressure and heart rate under various con-

TABLE 5 Prevalence of Definite or Possible Hypertension and/or Coronary Disease among the Parents of Smokers Compared with Nonsmokers

Parental History in Regard to Hypertension and/or	Nons	mokers	Sm	okers	Te	otal
Coronary Disease	N	%	N	%	N	%
One or both parents with posi- tive, questionable or un- known history	147	47.9	187	57.2	334	52.7
Both parents free from these disorders	160	52.1	140	42.8	300	47.3
Total	307	100.0	327	100.0	634	100.0

 $X_1^2 = 5.47 \quad P = 0.02.$ Nonsmokers = categories 0 and 1, table 1. Smokers = categories 2 through 8, table 1.

Comparison of Mean Recumbent Values of Blood Pressure and Heart Rate under Different Conditions for Nonsmokers, and Two Groups of Regular Cigarette Smokers TABLE 6

			Ž	Nonsmokers	Z.			Light	Light-and-Moderate Cigarette Smokers	oderate			Heavy C	igarette	Heavy Cigarette Smokers	70.
Conditions	Medalitements	2	Mann	S.E.	Ka	Kange	2	Mann	S.E.	Ra	Range	2	Mann	S.E.	Ra	Range
			Mean	Mean	Low	High	4	Media	Mean	Low	H.64	,	Mean	Mean	Low	High
. Casual readings on admis-	Systolic pressure	297	123.4	.78	06	170	113	122.3	1.28	96	160	127	123.0	1.32	06	170
sion physical examination	Diastolic pressure	297	74.7	.51	20	108	113	74.0		20	96	171	74.4		200	110
	Pulse pressure	297	48.0	60	90	001	113	**************************************		20	13	127	5.5		50	90
	Heart rate	283	76.80.0	.57	48	110	108	79.3*		48	114	170	79.50		00	108
. Initial observations in	Systolic pressure	290	119.0	.70	06	158	110	119.6	1.05	06	158	123	120.7	1.03	65	160
physiologic laboratory	Diastolic pressure	290	70.0	.50	44	66	110	1.69	.79	48	65	123	69.2		20	100
	Pulse pressure	290	49.10	.62	24	82	110	50.5	86.	22	700	123	51.5		20	80
	Heart rate	287	76.6d.r	99.	48	1112	107	80.5d	1.25	25	114	122	81.14		48	108
. Control observations be-	Systolic pressure	286	1111.1	.63	70	144	110	110.2	.94	80	132	122	111.3	.82	06	140
fore cold pressor test, ap-	Diastolic pressure	286	10.69	.46	80	96	110	67.5	.74	80	98	122	67.14		46	86
proximately 15 minutes after B	Heart rate	279	72.28	.62	20	104	108	74.2	66.	48	96	121	75.1s		48	96
. Greatest change observed	Systolic pressure	286	+11.6	.51	-12	+44	110	+11.0	69.	9-	+36	122	6.6+		+-	+38
during cold pressor test	Diastolic pressure	286	+13.8	.57	01-	+50	110	+12.7	.81	-2	+36	122	+12.2		0	+42
	Heart rate	273	+5.2	.58	-20	+52	100	+3.8	.67	-20	+22	119	+3.7		-26	+36
E. Control observations be-	Systolic pressure	287	110.4	09.	84	154	108	110.0	98.	80	132	121	110.2		06	138
before exercise test, ap-	Diastolic pressure	287	69.2h	.48	20	96	108	68.2	.74	20	06	171	67.2b		488	90
proximately 15 minutes	Pulse pressure	287	41.21	.52	20	64	108	41.8	.87	26	99	171	43.0	.74	20	62
after D	Heart rate	286	70.6	.68	4.3	114	106	71.8	1.10	45	103		73.11		48	94
F. Changes immediately	Systolic pressure	287	+32.6	69.	9+	+74	108	+32.1	1.26	+8	+100		+31.7	1.16	9+	+70
after exercise	Diastolic pressure	287	-1.3	.46	-26	+32	108	-2.3	.75	-34	+16	121	-2.1	69.	-28	+18
	Pulse pressure	287	+33.9	.78	+-	+70	108	+34.4	1.44	9+	+112		+33.9	1.34	4-	+84
	Heart rate	277	+21.1	.79	1.3	+82	102	+20.9	1.32	0	+9+		+20.4	1.11	9-	+55
3. Control observations be-	Systolic pressure	15	114.0	1.06	96	144	25	115.6	2.42	100	158	32	112.5	1.46	92	135
fore ballistocardiographic	Diastolic pressure	75	72.5	.86	54	90	25	72.7	1.64	09	66	32	72.4		09	85
smoking test	Pulse pressure	13	41.4	80	24	99	25	43.0	1.90	30	70	32	40.1		28	588
1	Heart rate	74	67.1×	1.09	47	94	25	68.6	2.31	44	16	32	71.9k	1.93	51	93
I. Changes immediately	Systolic pressure	7.4	+4.6	10.	90	+20	25	+3.5		90	+20	32	+2.6		100	+10
after smoking one cigarette	Diastolic pressure	74	+5.4	09.	9-	+20	25	+6.6		-4	+10	32	+3.6		14	+14
	Pulse pressure	74	-0.8	.71	+11	+20	25	-3.1		91-	+10	32	-1.0		-14	+8
	Hanet rate	2.4	2 4 1	0.0	100	1 3/1	30	100	4 63 79	0	1.20	2.3	163		6.	1 32

Comparisons which were statistically significant (P ≥ .05 is considered to be significant);

h .01 < P < .02 i .02 < P < .05 j .02 < P < .05 k .02 < P < .05 Nonsmokers versus heavy smokers P < .01 .02 < P < .05 P < .001 P = .02 P < .01 Nonsmokers versus light-and-moderate smokers a .02 < P < .05 d P < .01

Light-and-moderate smokers versus heavy smokers

Nonsmokers = categories 0 and 1, table 1. Light-and-moderate smokers = categories 2 and 3, table 1.

S.E. Mean = standard error of the mean =  $\frac{s}{\sqrt{N}}$  where s is the deviation of the distribution, computed from ungrouped data, and N is the total number of observations. Calculation of the pulse pressure is omitted from the cold pressor test. The greatest changes recorded in systolic and in distolic pressure did not necessarily occur at the same blood pressure reading; two readings were taken during the test.

ditions (table 6). These included casual measurements recorded at admission physical examination, initial readings at the start of a series of physiologic tests, control readings when the blood pressure and heart rate had stabilized after a short period of recumbency for the cold pressor test, the double Master exercise test and the ballistocardiographic smoking test, as well as the changes recorded during or immediately after the three kinds of stress test.\* 4, 8, 11 In these studies the measurements of the nonsmokers were compared with those of two groups of cigarette smokers: the light-and-moderate and the heavy. While the differences between the three groups were not great, some were significant:

1. Under casual, initial and control conditions the mean heart rate of the heavy smokers was in every instance significantly higher than that of the nonsmokers (A, B, C, E, G). Under casual conditions and at initial readings, the mean heart rate of the light-and-moderate smokers was also significantly higher than that of the nonsmokers (A, B). There was an increase in heart rate in going from nonsmokers to light-and-moderate

smokers to heavy smokers.

2. Significant differences between heavy smokers and nonsmokers were found in regard to diastolic pressure, pulse pressure or both at the initial readings and at both control readings during the series of physiologic tests (B, C and E). The mean pulse pressure of the heavy smokers was wider (B and E) and the mean diastolic pressure lower (C and E) than were the corresponding measurements for nonsmokers. Significant differences were not found between the smoker and the nonsmoker groups in regard to systolic pressure, or in any of the mean blood pressure measurements, either under casual conditions or in the control readings before the smoking test (A and G).

3. There were no significant differences between the smoking habit groups in the degree of change in blood pressure or heart rate during cold,

after exercise or after smoking (D, F and H).

4. All of the mean changes for each blood pressure and heart rate measurement during cold, after exercise or after smoking (D, F and H) were significantly different from zero for each of the three smoking habit groups, with the exception of the mean change in pulse pressure after smoking for nonsmokers and for heavy smokers (H).

5. There was considerable individual variation within each smoking

habit group.

The circulatory data for the women were looked at independently. They showed a trend toward higher mean heart rates among smokers compared with nonsmokers similar to that shown by the entire group. The inclusion

<sup>\*</sup>The cold pressor test and the exercise test were carried out on the same day; a routine electrocardiogram was taken between the two tests. The ballistocardiographic smoking test was performed on a different day, usually some months later. The number of subjects in table 6 G and H is smaller than in A through F because the ballistocardiographic smoking test was not performed on the classes of 1948 through 1952.

of a small number of women did not appear to influence the results recorded in table 6 in any important way.

# C. Metabolic Characteristics of Smokers and Nonsmokers:

## 1. Total serum cholesterol level.

In the classes of 1948 through 1957, one or more cholesterol determinations were carried out by a modification of the Bloor method on each of 612 subjects while in medical school.<sup>9</sup> When former smokers and those with unknown smoking habits are eliminated, the remaining 521 subjects were almost equally divided between regular smokers and nonsmokers. A significant association between the habit of smoking and higher cholesterol levels has already been reported by us.<sup>13</sup> When the subjects were grouped according to the highest cholesterol level observed for each individual, the percentage of smokers was smaller than the percentage of nonsmokers at the lower cholesterol levels (under 250 mg. per 100 c.c.), while smokers

Table 7

Relationship of Serum Cholesterol Level to Smoking Habits in Men

Highest Cholesterol in	Male	Male	Total Male		t of Total
mg. per 100 c.c.	Smokers	Nonsmokers	Subjects		Subjects
				Smokers	Nonsmokers
Under 250	135	157	292	46.2	53.8
250 or above	110	75	185	59.5	40.5
All levels	245	232	477	51.4	48.6

 $X_1^2 = 7.9$  P < 0.01. Nonsmokers = categories 0 and 1, table 1. Smokers = categories 2-8, table 1.

predominated over the nonsmokers at the higher cholesterol levels (250 mg. per 100 c.c. or above). A systematic gradation was found in the proportion of smokers to nonsmokers at different cholesterol levels. The highest proportion of smokers occurred among the 48 subjects with hypercholesterolemia,\* 62.5% of whom were smokers and 37.5% nonsmokers. In a fourfold table, with 250 mg. per 100 c.c. as the cutting point between "lower" and "higher" cholesterol levels, the association between the habit of smoking and higher cholesterol levels was significant at the 2% level. Table 7 gives the frequency of occurrence of higher cholesterol levels in male smokers compared with male nonsmokers. The positive association between higher cholesterol levels and smoking is again present, and indeed is strengthened by the exclusion of the 44 women, reaching a level of significance of p < 0.01.

# 2. Body weight.

The nonsmokers were compared with the entire group of smokers in regard to body weight. The percentage that each subject was overweight

<sup>\*</sup> Cholesterol of 300 mg. per 100 c.c. or above.

or underweight in relationship to his total body weight was calculated from standard tables. As shown in table 8, the percentage distribution of overweight and underweight was similar for smokers and nonsmokers, except at the upper end of the distribution curve. There was an excess of smokers who were 30% or more overweight, and the six subjects who were 40% or more overweight were all regular smokers. Among the 13 smokers (4.1%) who were 30% or more overweight, there were four light-and-moderate cigarette smokers, three heavy cigarette smokers, four mixed smokers and two who smoked pipes. When the weight categories are combined into four groups instead of eight, as in the right hand column of table 8, the difference between smokers and nonsmokers found by the chi-square test just attains statistical significance (P = .05).

Table 8
Relationship of Body Weight to Smoking Habits

Overweight and Underweight	Percentage			
Expressed in Percentage of Total Body Weight	Nonsmokers (N = 297)	Smokers (N = 321) %	Total (N = 618)	Grouping fo
+40 or above	0.0	1.9	1.0	1
+30 through +39	0.7	2.2	1.5	
+20 through +29	4.4	3.7	4.0	2
+10 through +19	16.2	15.6	15.9	
0 through +9	34.3	35.2	34.8	3
-1 through -9	29.3	28.7	29.0	
-10 through -19	13.8	11.8	12.8	4
-20 or more	1.4	0.9	1.1	
Total	100.1	100.0	100.1	

 $X_3^2 = 7.98$  P = .05. Nonsmokers = categories 0 and 1, table 1. Smokers = categories 2-8, table 1.

Table 9 gives the percentage distributions for male nonsmokers and for several groups of male smokers when the ponderal index, or height over the cube root of weight, is used as the criterion of body weight. The general picture is similar to that shown in table 8 by the entire group of men and women in regard to percentage who were overweight or underweight. "Other smokers" predominate among those of unusually heavy build.

# D. Psychologic Traits of Smokers versus Nonsmokers:

# 1. Habits of nervous tension.

As part of the habit survey, information has been obtained as to the subject's reactions to situations of stress, such as competitions, examinations

and family situations. From a list of 25 types of response, each student was asked to select all which were characteristic of him. Among the first 396 surveys previously reported, there were, on the average, 5.6 responses per student; the frequency of the various responses given ranged from 79% for general tension to 1% for vomiting.<sup>5</sup> The habits of nervous tension of 298 cigarette smokers and 302 nonsmokers are compared in table 10. As previously noted, the six usual responses were general tension, increased activity, uneasy or anxious feelings, increased difficulty in sleeping, loss of appetite and urinary frequency. The proportion of positive responses for the usual types of reaction under stress was similar in the two groups. Several sig-

Table 9
Relationship of Ponderal Index of Male Subjects to Smoking Habits

		Percentage Distribution of Ponderal Indices								
Body Build	Ponderal Index Ht./ $\sqrt[3]{\text{wt}}$ .	Nonsmokers (N = 265)	Total Smokers (N = 295)	Light-and- Moderate Cigarette Smokers (N = 101)	Heavy Cigarette Smokers (N = 118)	Other Smokers (N = 76				
Nonectomorphy	9.85-11.79	0.8	2.7	1.0	1.7	6.6				
	11.80-12.04	2.3	2.7	3.0	0.8	5.3				
	12.05-12.29	3.8	2.4	1.0	4.2	1.3				
Intermediate	12.30-12.54	11.3	8.5	8.9	10.2	5.3				
	12.55-12.79	12.8	13.6	18.8	8.5	14.5				
	12.80-13.04	22.3	25.8	30.7	23.7	22.4				
	13.05-13.29	22.6	19.3	14.9	23.7	18.4				
	13.30-13.54	11.3	12.5	10.9	13.6	13.2				
Ectomorphy	13.55-13.79	6.0	9.5	5.9	11.9	10.5				
	13.80-14.04	5.3	1.4	2.0	0.8	1.3				
	14.05-14.80	1.5	1.7	3.0	0.8	1.3				
Tot	al	100.0	100.1	100.1	99.9	100.1				

Nonsmokers = categories 0 and 1, table 1.

Total smokers = categories 2-8, table 1.

Light-and-moderate smokers = categories 2 and 3, table 1.

Other smokers = categories 5-8, table 1.

nificant differences were found, however, among the unusual and rare responses: anger and increased urge to eat occurred more often under stress among the smokers than among the nonsmokers. These differences were significant at the 1% level. Tremulousness and exhilaration were also more frequently reported by the smokers, but only the former approached the 5% level of significance. Decreased activity when under stress was the only trait occurring enough oftener among the nonsmokers than the smokers to attain the 5% level of significance. Urge to sleep, diarrhea, tendency to check and recheck work, urge to be alone, nausea and vomiting were also slightly more frequent among the nonsmokers. All of the other responses were found a little more frequently among the smokers.

TABLE 10 Percentage of Cigarette Smokers and of Nonsmokers Reporting Each Habit of Nervous Tension

Habits of Nervous Tension	Cigarette Smokers (N = 298)	Nonsmokers $(N = 302)$	Total (N = 600)
1. Exhaustion	12.4	11.3	11.8
2. Exhilaration	24.2	18.9	21.5
3. Depressed feelings	21.1	17.9	19.5
4. Uneasy or anxious feelings	47.0	41.7	44.3
5. General tension	82.2	77.8	80.0
6. Increased activity	68.1	66.2	67.2
*7. Decreased activity	3.4	7.0	5.2
8. Increased urge to sleep	9.7	11.9	10.8
9. Increased difficulty in sleeping	45.3	40.7	43.0
†10. Increased urge to eat	21.8	11.3	16.5
11. Loss of appetite	38.9	38.4	38.7
12. Nausea	4.0	4.6	4.3
13. Vomiting	1.0	1.3	1.2
14. Diarrhea	13.4	16.2	14.8
15. Constipation	6.0	5.0	5.5
16. Urinary frequency	29.9	28.8	29.3
17. Tremulousness	21.5	15.6	18.5
†18. Anger	27.2	17.2	22.2
19. Gripe sessions	16.4	12.6	14.5
20. Concern about physical health	4.4	3.3	3.8
21. Tendency to recheck work	24.2	25.5	24.8
22. Urge to confide	29.2	26.2	27.7
23. Urge to be alone	18.1	20.2	19.2
24. Irritability	8.7	8.6	8.7
25. Philosophic effort	22.5	20.5	21.5

\* = p < .05 † = p < .01.

Nonsmokers = categories 0 and 1, table 1.
Cigarette smokers = categories 2, 3, and 4, table 1.
In the questionnaire given to the students, some of the items are further defined. For example, general tension is defined as "keyed up" feelings—difficulty in becoming relaxed.

# 2. Rorschach studies.

Individual Rorschach tests have been carried out on the medical students as part of the long-term study.3,6 The tests were scored according to the Beck technic and the scores transferred to IBM cards. At the time of these

TABLE 11 The Percentage of Smokers and Nonsmokers Showing Varying Degrees of Productivity

Total Number of Responses to 10 Rorschach Cards	Percentage									
	Cigarette	Smokers	Other	All	Nonsmokers	Total Subjects				
	1-19/Day	20+/Day	Smokers	Smokers						
< 20	21.3	28.2	16.7	23.0	18.7	21.0				
20-39	45.7	33.0	40.0	39.3	42.2	40.7				
40-59	20.2	24.3	28.3	23.7	21.3	22.6				
60-79	9.6	12.6	8.3	10.5	10.2	10.4				
80 or over	3.2	1.9	6.6	3.5	7.6	5.4				
Number of subjects	94	103	60	257	225	482				

preliminary tabulations, the data from eight medical school classes were available for analysis. Only a small number of the Rorschach variables under study will be considered in the present smoker-nonsmoker comparisons. The use of the Rorschach test in this type of study is rare enough to warrant detailed statistical analysis of our findings.

The relationship of smoking habits to productivity in the intellectual sphere was first examined. Productivity (R) is measured by the total number of responses to the 10 test cards. Table 11 shows that there was no substantial difference in the frequency distribution of the total number of responses of smokers compared with nonsmokers, whether the latter were compared with the total group of smokers or with two subgroups of cigarette smokers and with the other smokers. Among the heavy smokers (20 or more cigarettes a day) there did seem to be a trend toward a brief Rorschach

TABLE 12 Relationship of Academic Standing to Smoking Habits

	Percentage										
Academic Standing	Cigarette	Smokers	Other	All	Nonsmokers	Total Subjects					
	1-19/Day	20 +/Day	Smokers	Smokers							
Very high High	18.8 41.6	13.5 41.4	12.1 34.5	15.2 39.9	13.6 33.9	14.5 37.2					
Medium Low Very low	25.7 12.9 1.0	32.7 11.5 1.0	36.2 17.2 0.0	30.8 13.3 0.8	37.6 12.7 2.3	33.9 13.0 1.5					
Number of subjects	101	104	58	263	221	484					

Nonsmokers = categories 0 and 1, table 1.

Cigarette smokers = categories 2, 3, and 4, table 1. Other smokers = categories 5, 6, 7 and 8, table 1.

All smokers = categories 2-8, table 1.

protocol (under 20 responses) and away from a very large number of responses (80 or more), but the number of subjects involved is small. similarity of smokers and nonsmokers as to productivity in the Rorschach test is paralleled by the findings in regard to academic standing. The students' academic standing at the end of four years' work was classified on a five-point scale ranging from very high to very low. Table 12 shows that there is no substantial difference between smokers and nonsmokers in regard to academic excellence. If anything, smokers appear to have a slight edge over nonsmokers in the high and very high academic groups.\*

Further studies of the total number of responses revealed inconsistencies in the frequency distribution of R for successive classes of students.

<sup>\*</sup> Slight differences in the number of subjects in tables 11 and 12 arise from the fact that a few subjects graduated without taking a Rorschach test, while a few who took the Rorschach test did not graduate.

arose from the fact that some of the clinical psychologists administering the Rorschach tests had different ranges for R than did others. In the early years, tests were administered by Psychologists A, B and C, a woman and two men, who were closely supervised by the same Rorschach expert. Their ranges for R were similar and the data from their protocols were pooled. In the middle years, psychologists D and E, a husband and wife, who had been trained elsewhere, administered the tests. The ranges of R for their data were similar to each other but considerably different from

Table 13

Comparison of the Number of Responses (R) to the Rorschach Test for Nonsmokers and for Cigarette Smokers

Number of Responses -	Psycholo	gists A, B, C	Psychol	ogists D, E
Number of Responses	Nonsmokers	Cigarette Smokers	Nonsmokers	Cigarette Smokers
5-9	0	0	3	4
10-14	0	1	18	26
15-19	4	3	15	20
20-24	3	3 3 3	17	8
25-29	9	3	12	13
30-34	11	10	9	10
35-39	6	17	4	4
40-44	8	2	5	6
45-49	8 2 3	2 7	5 3	1
50-54		9	2 3	4
55-59	8	4	3	3
60-64	6 3 3 2 2	9	0	1.
65-69	3	2	2	2
70-74	3	2 2 3	1	0
75-79	2	3	0	0
80-84	2	0	1	0
85-89	1	0	1	0
90-94	2	0	0	1
95+	4	3	3	0
Total	77	78	99	103
Mean	49.08	46.68	29.62	25.64
S.E.M.	2.58	2.13	2.08	1.56

Nonsmokers = categories 0 and 1, table 1. Cigarette smokers = categories 2, 3, and 4, table 1.

those of Psychologists A, B and C. This contrast is shown in table 13.\* Despite the difference in the distribution of R for the two groups of psychologists, there was no significant difference between smokers and non-smokers as to the means for R in either group. In each instance the non-smokers gave a few more responses on the average than did the smokers, with a greater scatter about the mean. If deviations from the means are computed for each of the two groups of psychologists and the resulting

<sup>\*</sup>The range for a smaller number of protocols administered in later years by Psychologists F and G, both men, was intermediate, and is not shown in table 13.

TABLE 14

Comparison of Rorschach Constriction to be Found among Nonsmokers, Moderate Smokers and Heavy Smokers, for Two Groups of Psychologists

Psycholo- gists	Rorschach	Nonsmoker	Light-and- Moderate Smoker	Heavy Smoker	Total	$X_1^2$	P			
A, B, C	Constricted 9 Expanded 68 Total 77							.34	>.80	
D, E	Constricted Expanded Total	20 79 99	9 43 52	14 37 51	43 159 202	1.71	>.30			

X2 with one degree of freedom was calculated by combining light-and-moderate and heavy smokers into a single group for comparison with nonsmokers.

Nonsmokers = categories 0 and 1, table 1. Light-and-moderate smokers = categories 2 and 3, table 1.

data combined, there is a slightly higher proportion of responses above the mean for nonsmokers compared with smokers. This difference between smokers and nonsmokers is not significant, however, by the chi-square test.

The degree of Rorschach constriction according to smoking habits was next examined (table 14). Constriction was considered to be present if the total of movement and sum color responses was two or less; if these responses numbered three or more, the Rorschach protocol was termed expanded. When the Rorschach tests of the two groups of psychologists were compared, differences in the proportion of constricted protocols were

TABLE 15

Comparison of Distributions of Proportions of Whole (W), Detailed (D) and Very Detailed (Dd) Responses to Rorschach Test among Students with Different Smoking Habits, for Two Groups of Psychologists

Rorschach Determinants			Psycho	ologists A	Psychologists D, E								
		Heavy Smokers	Light- and- Moder- ate Smokers	Non- smokers	Total	X42	P	Heavy Smokers	Light- and- Moder- ate Smokers	Non- smokers	Total	X42	P
W's	Low Normal Marked Very marked Total	11 10 8	18 16 14 48	33 21 23 77	62 47 45 —	0.7	,95	6 11 16 18 51	12 10 28 54	13 19 30 37 99	23 42 56 83 204	4.6	>.30
D's	Low Normal Marked Total	7 18 4 29	11 27 10 48	27 26 24 77	45 71 38 154	12.4	<.02	22 18 11 51	32 14 8 54	47 42 10 99	101 74 29 204	7.4	>.10
Dd's	Low Normal Marked Total	13 8 8 29	24 15 9 48	38 20 19 77	75 43 36 154	1.1	>.80	43 6 2 51	44 9 1 54	71 22 6 99	158 37 9 204	3.6	>.30

<sup>[ ]</sup> Indicates groups combined for X3.
Nonsmokers = categories 0 and 1, table 1.
Light-and-moderate smokers = categories 2 and 3, table 1.

found, as would be anticipated in view of the marked differences in R noted above. However, there was no significant difference in constriction between the smokers and the nonsmokers tested by either group of psychologists.

Similarly, the distribution of the proportions of whole (W), detailed (D) and very detailed (Dd) responses to the Rorschach test was analyzed according to smoking habits and the two main groups of psychologists (table 15). The mode of approach is one of the concepts based on these three variables, and obsessive-compulsive trends are measured by the degree

Table 16

Comparison of Distributions of Numbers of Pure Color (C), Color Form (CF) and Form Color (FC) Responses to Rorschach Test among Students with Different Smoking Habits, for Two Groups of Psychologists

		Psych	ologists A,	В, С			Psyc	hologists D	, E	
Rorschach Deter- minant	No. of Re- sponses	Heavy Smokers	Light- and- Moderate Smokers	Non- smokers	Total	No. of Re- sponses	Heavy Smokers	Light- and- Moderate Smokers	Non- smokers	Tota
	0	14	25	47	86	0	47	46	88	181
	1	10	15	14	39	1	3	6	10	19
C	2 3+	4	6	10	20	2	1	0	1	2
	3+	1	2	6	9	3+	0	0	0	0
	Total	29	48	77	154	Total	51	52	99	202
	0-1	14	21	30	65	0	18	25	38	81
Í	2-3	8	11	25	44	1	16	12	36	64
	4-5	6	11	- 13	30	2	10	6	12	28
CF	6+	1	5	9	15	3	6	7	5 8	18
						4+	1	2	8	11
	Total	29	48	77	154	Total	51	52	99	202
	0-1	12	24	34	70	0	29	25	51	105
	2-3	8	13	24	45	1	13	17	26	56
	4-5	8 7 2	6 5	9	22	2 3	5 4	8	13	26
FC	6+	2	5	10	17		4	0	5	9
						4+	0	2	4	6
	Total	29	48	77	154	Total	51	52	99	202

X<sup>2</sup> Tests with various degrees of freedom showed no differences in the numbers of C, CF or FC responses given by heavy, light-and-moderate and nonsmokers.

Nonsmokers = categories 0 and 1, table 1. Light-and-moderate smokers = categories 2 and 3, table 1.

of overemphasis upon rare or minute details. For psychologists D and E there was no significant difference between smokers and nonsmokers in the proportions of W, D or Dd responses. For psychologists A, B and C, the only significant difference between smokers and nonsmokers occurred in the proportions of D, where excesses of both low and marked D responses were noted among the nonsmokers.

The color responses are thought to reflect the emotional sphere of the human personality. There were no important differences in the numbers of

pure color (C), color form (CF) or form color (FC) responses of non-smokers, light-and-moderate smokers and heavy smokers for either psychologists A, B and C or psychologists D and E (table 16). It was necessary to use different scales for the two groups of psychologists to take care of the differences in range of response. Chi-square tests were carried out for all portions of table 16, using one or more degrees of freedom by com-

Table 17

Comparison of Number of S Responses Given by Smokers and by Nonsmokers
Tested by Three Groups of Psychologists

Psycholo-	No. of Subject	nt a						Nur	mber	of S	Respo	nses				
gists	No. or Subject	is.	0	1	2	3	4	5	6	7	8	9	10	11	12	13+
A, B, C	Smokers Nonsmokers	81 77	7 4	15 11	14 14	13 11	10	5 7	3 5	5 4	2 3	1 2	2 2	0	1	3
D, E	Smokers Nonsmokers	115 98	38 25	39 41	14 13	13 7	6 2	1 6	1 0	1	0 2	0	1 0	0	0	1 0
F, G	Smokers Nonsmokers	28 34	5 5	2 5	4 3	3 4	5	0 2	2 2	1 3	1 2	4 4	1	0	0	0

				4.5.					
				Summary of Number of S Responses					
			0-2		3-5		6 or More		
			N	%	N	%	N	%	
A, B, C	Smokers Nonsmokers	81 77	36 29	44.4 37.7	28 27	34.6 35.1	17* 21*	21.0 27.3	
D, E	Smokers Nonsmokers	115 98	91 79	79.1 80.6	20 15	17.4 15.3	4 4	3.5 4.1	
F, G	Smokers Nonsmokers	28 34	11 13	39.3 38.2	8 7	28.6 20.6	9* 14*	32.1 41.2	

			Summary of Num	ber of S Respons	es
		0	-5	6 or	More
		N	%	N	%
All psycholo- gists	Smokers 224 Nonsmokers 209	194 170	86.6 81.3	30 39	13.4 18.7

<sup>\*</sup>  $X_1$ ° for 6 or more responses compared with 5 or less shows that there is no significant difference for either A, B, C or F, G groups.

For Part C,  $X_1^2 = 2.26$  P = .02.

Nonsmokers = categories 0 and 1, table 1.

Smokers = categories 2-8, table 1

bining the subgroups in various ways, but in no case were the differences found to be statistically significant.

The white space determinants (S) in the Rorschach protocol are said to indicate resistance. S responses are thought to be "one of the chief structural indices of healthy aggression in a strong personality, and of hostility or negativism in a weak, unhealthy one." In table 17A the distributions of smokers and nonsmokers by number of S responses are very similar in all three groups classified by psychologists.\* When the distributions are summarized in table 17B, nonsmokers appear to be a little more likely to give a high number of S responses (six or more) than are smokers. While this difference is not great enough to be statistically significant for any of the three groups when the smokers and nonsmokers are subdivided according to psychologist, it is significant when the responses for all the smokers are pooled and compared with the pooled data for all the nonsmokers, without regard to the psychologist administering the test  $(X_1^2 = 2.26, p = .02)$  (table 17C).

Table 18

Four-way Grouping of Healthy Subjects as a Basis for Preventive Measures against Hypertension (H+) and/or Coronary Heart Disease (C+)

Group	Significan	Probability of Developing Disease	
Group	Parental H+/C+	Individual Traits	Disease
I	+	+	High
11	_	+	Fairly high
111	+	-	Doubtful
IV	-	-	Low

F. Comparative Frequency of Smokers and Nonsmokers among Subjects with Different Degrees of Susceptibility to Hypertension and/or Coronary Heart Disease: A four-way grouping has been described for use in screening healthy young adults to find those who are highly susceptible to hypertension and coronary disease. This grouping, shown in table 18, is based on both the subject's own characteristics (including cholesterol level, body weight and build, blood pressure, heart rate and circulatory hyperreactivity to stress) and his parental history. Subjects in Group I, in whom both the familial and the individual factors are positive, are thought to be much more susceptible to the diseases in question than are subjects in Group IV, in whom these factors are negative. Those in Groups II and III are believed to be intermediate in regard to susceptibility.

When the smoking habits of the four groups of subjects were examined, more smokers than expected were found among the subjects in Group I,

<sup>\*</sup>The findings on the group of protocols administered by Psychologists F and G have been included in this table because of the borderline nature of this difference.

the highly susceptible group (table 19). Conversely, there were fewer smokers than expected in Group IV, the least susceptible group. The numbers of smokers observed in Groups II and III, the intermediate groups, corresponded closely to the numbers expected. When Groups II and III are eliminated, and chi-square with one degree of freedom is calculated for

Table 19

The Proportion of Smokers among 340 Healthy Subjects Grouped According to Probable Susceptibility to Future Hypertension and/or Coronary Heart Disease (H+/C+)

Four-way N	Susceptibility to H+/C+		okers = 168)		nokers 172)	
			Obs.	Exp.	Obs.	Exp.
I II III IV	74 72 65 129	High Intermediate Intermediate Low	45* 35 34 54*	36.6 35.6 32.1 63.6	29* 37 31 75*	37.4 36.4 32.9 65.4

\*  $X_{1^2} = 6.8$  p < 0.01.

Nonsmokers = categories 0 and 1, table 1. Smokers = categories 2-8, table 1.

smokers and nonsmokers in Groups I and IV, the difference is significant at the 1% level (table 19).

## DISCUSSION

These studies have approached the problem of smoker-nonsmoker differences on a very broad front. The findings should therefore be taken as highly suggestive rather than conclusive, even when statistical significance is demonstrated in a given comparison. It is well known that where a large number of variables is examined, some will achieve significance by chance alone. The exact delineation of the characteristics of smokers compared with nonsmokers therefore awaits further critical study and evaluation.

Several reports on smoker-nonsmoker comparisons are already at hand, however, which tend to support these studies. Friberg et al. have compared the smoking habits of 59 pairs of adult monozygotic twins with an equal number of dizygotic twins matched as to age and sex. They found significantly greater concordance within the monozygotic pairs. Fisher reported some preliminary observations on the smoking habits of German twins which pointed in the same direction. While these findings are consistent with the hypothesis that smoking habits are influenced by genetic factors, the possibility brought forward by Bleuler that the environment of monozygotic twins may be more uniform than that of dizygotic twins must not be overlooked.

In 1959, Karvonen et al. reported observations made in Finland on the relationship of smoking habits to cholesterol level, blood pressure and body fatness.<sup>19</sup> Samples of men, aged 20 to 59 years and totaling 360 smokers

and 165 nonsmokers, were studied in two rural and one urban area. The over-all mean cholesterol level of the smokers was significantly higher than that of the nonsmokers: only in the 50 to 59 age group from rural areas were significant differences not found. Thus their studies substantiate our observation of a significant difference in cholesterol level between young adult smokers and nonsmokers, with the smokers showing higher levels.13 The significance of our original findings is heightened when the comparison is limited to men (table 7). The same investigators found that Finnish smokers had slightly lower mean systolic, diastolic and pulse pressures than did nonsmokers. Their observations agree with ours except in regard to systolic pressure, where we found no significant difference. Intrinsic differences in the two population samples may well account for this disparity. In any event, the mean blood pressure differences in both studies were small. In regard to body weight, rural smokers in Finland were found to be slightly thinner than were rural nonsmokers, but there was no difference in weight between the urban groups. Their findings were based on skinfold measurements, while ours were based on standard weight tables and on the ponderal index. Despite the differences in method of measurement, one cannot say that the two studies show disagreement, because when the ponderal index in our series is examined, the distribution curves of the male cigarette smokers were the same as those of the male nonsmokers (table 9). These are the groups of our subjects which are comparable to the Finnish study, in which only male cigarette smokers and male nonsmokers were considered. It would seem, also, that the medical students represent an urban rather than a rural population.

Psychologic comparisons of smokers and nonsmokers have been reported by Heath and by Lilienfeld, but neither of them used the Rorschach test as a method of measurement.<sup>20, 21</sup> The questionnaire method was used by Lilienfeld, and he found that significantly more smokers than nonsmokers often "felt like smashing things for no particular reason," and also were more often "sore" when people told them what to do. These two items tend to agree with our finding that smokers react to situations of stress with anger more often than do nonsmokers. Heath looked into the occurrence of certain symptoms under stress, but found a significant difference between smokers and nonsmokers only in regard to frequency of urination. There was no difference among our subjects in regard to this question; the "habits of nervous tension" in which significant differences were found by us—namely, decreased activity, increased urge to eat, and anger—were not included in Heath's list of items.

After completion of these preliminary studies it is apparent that in most respects smokers and nonsmokers are very similar, and that the distribution curves of the two groups show a high degree of overlapping, even where statistically significant differences exist. In no instance did the distribution of smokers and nonsmokers approach a true bimodal curve. Therefore, any genetic differences between smokers and nonsmokers in the areas

explored in this study appear to be more readily explained on the basis of graded characteristics than of single gene differences.

### SUMMARY

- 1. Among Johns Hopkins medical students, smokers appeared to differ from nonsmokers in a number of ways. Significant differences noted in this preliminary survey were as follows:
  - a. Smokers, as a group:
    - (1) More often gave a history of parental hypertension.
    - (2) Had higher mean recumbent values for heart rate and pulse pressure.
    - (3) Had higher cholesterol levels when the highest values recorded for each subject were used as the basis of comparison.
    - (4) Had a larger proportion of heavy individuals.
    - (5) More often reported anger and an urge to eat when under stress.
  - b. Nonsmokers, as a group:
    - (1) More often gave a history that both parents were free from hypertension and coronary disease.
    - (2) Had higher mean recumbent values for diastolic pressure.
    - (3) More often reported decreased activity under stress.
    - (4) More often gave a high number of white space responses in the Rorschach test.
  - c. A parallelism existed between the presence or absence of factors thought to indicate high susceptibility to hypertension and/or coronary disease, on the one hand, and the presence or absence of the habit of smoking, on the other. The highest proportion of smokers was found in the most susceptible group, Group I, and the lowest proportion of smokers was noted in the least susceptible group, Group IV. Groups II and III were intermediate in both respects.
- 2. Broad areas were found where the characteristics of smokers and nonsmokers appeared to be very similar. No significant differences were found:
  - (a) in the responses of blood pressure and heart rate either to the cold pressor test, to the double Master exercise test or to the ballisto-cardiographic smoking test;
  - (b) in academic excellence;
  - (c) in most of the Rorschach variables examined, including productivity, constriction, proportion of whole, detailed and very detailed responses, and distribution of color responses.
- 3. It cannot be determined from the present data whether those individual characteristics which are more often found among smokers than non-

smokers represent true constitutional differences or are due to the effects of smoking.

4. The differences observed in the parental histories indicate that smokers and nonsmokers have a somewhat different heritage, and suggest that at least some of the variations found in individual traits may be genetic in origin.

#### ACKNOWLEDGMENT

I should like to express my appreciation to Mary H. Burke and Frieda F. Eisenberg for their advice and help in regard to the statistical part of this paper.

#### SUMMARIO IN INTERLINGUA

Le habitudes fumatori de 10 consecutive classes de studentes de medicina a Johns Hopkins esseva studiate in relation con certe characteristicas genetic, physiologic, metabolic, e psychologic. Le fumatores differeva significativemente del non-fumatores in plure manieras. Prendite como gruppo total, le fumatores (1) reportava plus frequentemente le antecedente de hypertension in le parentes, (2) habeva plus alte valores medie pro le frequentia cardiac e le tension de pulso, (3) habeva plus alte nivellos de cholesterol, (4) includeva un plus alte proportion de individuos pesante, e (5) reportava plus frequentemente reactiones de vexation e del desiro de mangiar plus in situationes stressose. Le non-fumatores (1) reportava plus frequentemente que ambe le parentes esseva libere de hypertension e de morbo de arteria coronari, (2) habeva plus alte valores medie de tension diastolic, (3) reportava plus frequentemente un augmento de activitate in situationes stressose, e (4) respondeva plus frequentemente a base de spatios blanc in tests de Rorschach.

Il existeva un parallela inter le presentia o absentia de factores considerate como indicatores de alte grados de susceptibilitate de contraher hypertension e/o morbo coronari de un latere e le presentia o absentia del habitude del fumar del altere latere. Le plus alte proportion de fumatores esseva trovate in le gruppo le plus susceptibile (gruppo I); le plus basse proportion de fumatores esseva trovate in le gruppo le minus susceptibile (gruppo IV). Gruppos II e III esseva intermediari in ambe

respectos.

Esseva trovate large areas in que le duo gruppos non esseva significativemente differente. Le characteristicas de fumatores e non-fumatores esseva simile con respecto a (1) le responsas del tension de sanguine al test de pression per frigido, le duple test de exercitio de Master, e le test fumatori ballistocardiographic, (2) excellentia academic, e (3) le majoritate del variabiles de Rorschach examinate, incluse productivitate, constriction, proportion de responsas total e detaliate e multo detaliate, e le distribution del responsas de color.

Super le base del presente datos il non es possible determinar si le characteristicas individual que se incontra plus frequentemente inter fumatores que inter nonfumatores representa differentias constitutional o es causate per le effectos del fumar. Le differentias observate in le antecedentes parental indica que fumatores e nonfumatores differe in un certe mesura in lor hereditate e suggere que al minus certes del differentias trovate in tractos individual es de origine genetic.

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# SUSCEPTIBILITY AND IMMUNITY TO COMMON UPPER RESPIRATORY VIRAL INFECTIONS— THE COMMON COLD\*†

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Common upper respiratory viral infections, despite their frequency, have been something of an enigma to physicians and scientists in general. Little has been known about their specific etiology and the factors that influence susceptibility or resistance to infection. A prevalent view, even within recent years, has been that there is a common cold virus to which only man is susceptible, and which causes recurrent symptomatic infections without establishing immunity of the host. This concept now appears to be far too simple. Within the last decade, information has accumulated rapidly on the etiology of these common infections and the susceptibility of the host. Tissue culture technics have extended our knowledge of the viruses associated with respiratory illnesses. Controlled experiments with volunteers have permitted observations upon the susceptibility of man.

Viruses and families of related viruses, now numbering approximately 70, have been recovered from respiratory secretions of persons suffering with respiratory illnesses of varying severity. These viruses propagated in tissue cultures and some others associated with respiratory disease are given in table 1. Many of these agents do not produce the common cold as the classic or predominant manifestation of infection. Nevertheless, most if not all of them, and others in addition, can produce a common coldlike illness in some persons. Some of the viruses, as far as we know, cause only symptoms of a common cold; the majority of clinical colds undoubtedly result from infections with viruses of this type, of which only a few are known. Viruses referred to as NS agents are demonstrable as infectious material in the nasal secretions of a person suffering with a common cold, but attempts to identify and characterize them in vitro have not been successful.

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The present report gives observations collected over a seven- to eight-year period from the results of experimental challenge of volunteer subjects with one of the common cold agents under controlled conditions. It is concerned largely with the uncharacterized infectious agents in the nasal secretions from donors with naturally acquired, typical common colds. These have been shown to be several immunologically distinct viruses.¹ Considerable attention has been given to the experimental cold syndrome in volunteers, and the influence of the virus, the host and environmental factors upon susceptibility and the resulting clinical illness. The lack of relationship to chilling, the importance of certain physiologic and psychologic conditions, and the demonstration of specific immunity under controlled experimental

#### TABLE 1

Some Viruses Associated with Respiratory Illnesses in Humans

Myxoviruses:

Influenza A, B, C

Para-influenza 1 (Sendai HA II), 2 (CA), 3 (HAI), 4 (M. 25)
 Mumps, NDV.

Coxsackie Viruses A, B

Adenoviruses 1, 2, 5, 6; 3, 4, 7, 14

ECHO and ECHO-like Viruses

2060, JH (ECHO 28)

Reoviruses 1, 2, 3 (ECHO 10) 57-67 (ECHO-6), U Virus (ECHO-11), JU-1 (ECHO-20)

Other

Coe

Respiratory Syncytial (Long) CCA (Sue)

Common Cold NS Agents

Primary Atypical Pneumonia (PAP-Eaton)

Ornithoses

conditions are discussed. Some of the data have been reported in part previously.1-6

## MATERIALS AND METHODS

Infectious Nasal Secretions: Donors with naturally acquired typical common colds in the months from September to May have contributed specimens of several milliliters of nasal secretion. The secretions have been filtered free of bacteria and cells and stored at minus 90° F. They have been studied in animals and tissue cultures for the presence of known viruses. Secretions from six individual donors, collected in different years from 1953 to 1958, in which no known virus could be shown by laboratory tests, were infectious in volunteers and have been studied in many subjects.

Volunteers: Students ranging in age from 18 to 48, the great majority of whom were 21 to 25 years of age, have been challenged with a nasal secretion, usually diluted 100 times, a virus grown in tissue culture, or a control salt solution. The challenge was administered as nasal drops of 0.2 ml. in each nostril. The subject was not informed as to the nature of

the challenge solution instilled. Symptoms were recorded for each day of the following week by one other person, who also was uninformed as to the nature of the material given each volunteer. Whether the subject developed a cold was determined by two of three criteria: (1) the total symptom score from eight symptoms characteristic of the common cold, (2) an increase in nasal discharge on three or more days after challenge, and (3) the evaluation by the subject that he had developed a common cold. These procedures have been described in detail previously.<sup>2</sup>

## RESULTS

The Cold Syndrome Among Volunteers: Symptoms by which volunteers characterized their natural clinical colds are shown in figure 1. Nasal discharge was the symptom most uniformly recorded as a characteristic of a

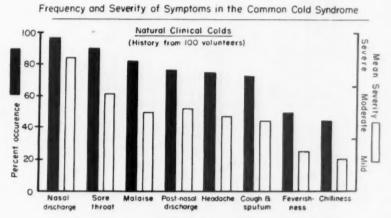


Fig. 1.

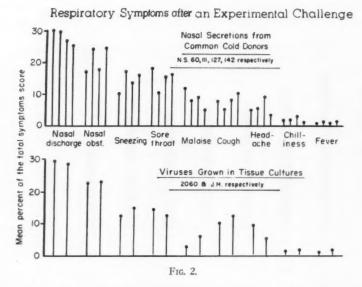
common cold. It was the only symptom that was rated as severe. Sore throat, malaise, postnasal discharge, headache, cough and sputum were frequent symptoms of moderate severity. Feverishness and chilliness were reported by less than one-half of the subjects as a characteristic of their naturally acquired colds, and both were of mild degree.

The nature of the illnesses produced in volunteers by the instillation of nasal secretions or by a challenge with a tissue culture harvest containing 2060 or JH viruses is shown in figure 2. The experimentally-induced infections closely resembled the typical common cold. Symptoms among volunteers on successive days after challenge with one virus (NS 69) are compared with symptoms among control subjects in figure 3 by plotting the statistical significance of the daily difference. Headache, chilliness, sneezing and sore throat were early symptoms, which usually subsided as nasal dis-

charge, obstruction and cough appeared and increased. The peak of the symptoms usually was reached three or four days after challenge, but varied with different secretions and in different persons. The illness was commonly over within one week, but approximately 40% of subjects had continuation of nasal symptoms into the second week after challenge.

As in natural colds, experimental infection was rarely accompanied by an elevation in temperature. Also, it was not possible to find objective signs of viral infection from examination of the nose and throat following an infectious challenge.

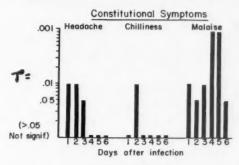
Laboratory evidence of infection with or without symptoms was observed by examination of epithelial cells scraped from the inferior nasal

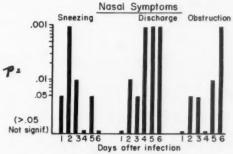


turbinates and stained by the method of Papanicolaou. As shown in figure 4, on the second, fourth and sixth days after the administration of an infectious secretion, there was an increase in the percentage of abnormal epithelial cells, analogous to the cytopathogenic effect observed in tissue cultures after inoculation with some viruses. No specific cellular characteristic of infection was recognized, but there was an increase in cells showing all degrees of nuclear and cytoplasmic degeneration, including eosinophilic cytoplasmic inclusions in some cells. The results in figure 4 also show subclinical infection of some subjects, and suggest that among those with symptoms the infection was more extensive.

Bacteriologic cultures of the nasal specimens before and on the fourth, seventh and ninth days after challenge were made for detection of pathogenic

# Significance of Daily Symptoms Among Subjects Infected with the Common Cold





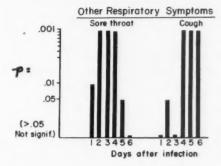
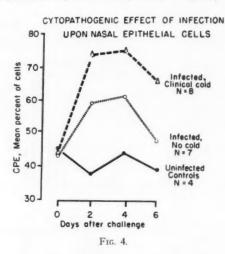


Fig. 3.

microörganisms in the respiratory secretions. Some of the volunteers harbored staphylococci, hemolytic streptococci or pneumococci in their prechallenge specimens. There was no apparent relationship between the presence of these microörganisms and the development of clinical symptoms. Neither was there an appreciable increase in the frequency with which these pathogenic microörganisms were recovered from specimens during nine days



after challenge. In contrast, viruses which were not found in prechallenge cultures were recovered from 24, 53 and 33% of the cultures, respectively, on days 2, 4 and 6 after challenge with IH virus.<sup>6</sup>

Infectivity and the Effect of the Virus on the Common Cold Syndrome: The infectious nasal secretions produced symptoms in only one third to one-half of the volunteers who received them as a challenge. As shown in table 2, secretions from the same donor (159) on the first or second day of coryza were equally infectious. Infectivity could be shown in the sediment lysed after washing, as well as in the supernatant component of nasal secretion. Dilution of the secretion over the range 1:10 to 1:100 caused no significant change in the frequency or severity of colds. In a dilution of 1:1000 or more, infectivity was markedly lower.

Differences in the clinical syndrome caused by different secretions are illustrated by the results given in table 3. For one, the incubation period

Table 2
Infectivity Characteristics of a Common Cold Virus in Nasal Secretion

Characteristic of Secretion	Number Observed	Per Cent with Colds
Day of Collection:		
First day of coryza Second day of coryza	19 167	36 37
Component of Secretion:		
Supernatant Sediment (lysed)	206 29	36 38
Dilution		
1:10 1:100 1:1000	58 89 30	33 36 11

before the onset of symptoms was 48 hours, for another 24 hours, and for the third, less than 24 hours. If symptoms were categorized as predominantly nasal, predominantly pharyngeal or predominantly constitutional, there was a difference in the frequency with which these syndromes were caused by challenge with each of the three secretions. Although the common cold syndrome was the most frequent and "flu" the most infrequent with each of the three infectious secretions, they appear to be three different viruses, if judged by the incubation period and spectrum of illness produced.

Constitutional and Psychologic Influences Upon the Cold Syndrome: If subjects reported particular symptoms as characteristic of their naturally acquired colds, they tended to report the same symptoms in experimental illnesses. Volunteers who classified their usual colds as "head colds" were more likely to report nasal symptoms without cough, whereas more subjects whose record of usual colds was the "head and chest" type of cold reported cough as a part of the experimental illness. Similarly, among subjects who considered themselves to be relatively resistant to respiratory illnesses, ex-

Table 3
Clinical Differences among Common Cold Viruses

			Pred	lominant Syndrome	. %	
Challenge Secretion	Incubation Period (hrs.)	Number of Volunteers with Illness	Nasal Discharge, Obstruction	Sore Throat, Hoarseness, Cough	Fever, Headache, Malaise	
			"Common Cold"	"Undiff. URI"	"Flu"	
NS 127 NS 142 NS 69	48 24 <24	111 97 62	97 80 61	3 19 38	0 1 1	

perimental colds developed less frequently than among subjects who considered themselves to be relatively susceptible.

The susceptibility of volunteers to naturally acquired colds is shown in figure 5, and is compared to the outcome from a single challenge under experimental conditions. Among approximately 2,500 subjects, the mode number of colds per year was two, and 85% reported one to three. Among a control group of volunteers who received uninfected buffer solution, there was a direct and statistically significant relationship between the usual number of colds per year reported by the subject and the likelihood of his developing symptoms of a cold in the experiment. Thus, among 23 subjects who reported five or more colds per year and who received the non-infectious control inoculum, 26% developed a cold according to the criteria used in the experiments. Among subjects who reported fewer natural colds and, received uninfected material, there was a proportionately smaller number of experimental colds. This was a progressive linear relationship between susceptibility to natural colds and the development of

symptoms of a cold following the nasal instillation of a small quantity of isotonic salt solution, and may be the result of vasomotor rhinitis, or the psychologic reporting of symptoms.

Such a constitutional proneness related to the number of natural colds was not apparent if the experimental challenge contained infectious virus.

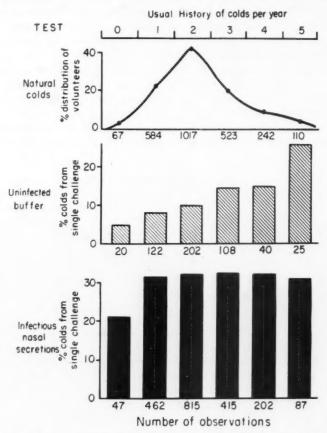


Fig. 5. Relationship of susceptibility to naturally acquired colds and the result of a single experimental challenge with uninfected or infectious material.

As shown in the bottom panel of figure 5, the frequency of experimental colds from an infectious inoculum was essentially identical among all volunteers who reported one or more colds per year. Thus, the proneness to natural colds did not appear to be an increased susceptibility to infections. One difference among volunteers challenged with an infectious secretion was a decreased frequency of experimental colds in persons who reported

no natural colds. This group also had the lowest frequency of cold symptoms following instillation of uninfected material. They appeared, therefore, to have a physical or psychologic resistance to illness.

Representative samples of volunteers were evaluated with respect to possible psychologic or attitudinal factors which might be related to symptom reporting under experimental conditions. As a group, the volunteers differ with respect to certain variables on the Edwards Personal Preference Schedule and the MMPI when compared with the standardized norms for these tests. These differences, however, seem to pertain to the characteristics of the general population from which our volunteers were drawn, and were not unique for the volunteer group. Of more importance are findings which suggest that individuals who are prone to manifesting or reporting symptoms under experimental conditions are significantly different psychologically from those who report no symptoms after challenge. Preliminary analyses indicate that these differences have to do with the individual's self-concept, degree of freedom from emotional stress, need for close interpersonal relationships, level of optimism or pessimism concerning one's future, and attitudes toward illness in general.

Attitudes exhibited before challenge showed that cold symptoms would be less likely to be reported by individuals who (1) did not believe they would develop a cold, (2) thought that emotional status did not influence physical status, and (3) reported feeling no concern or worry over anything going on in their lives at the time of experimental challenge. On the other hand, a positive response to these three attitudes made it more likely that cold symptoms would be reported by the individual. Analysis of interview material also suggests that individuals who are undergoing particular emotional stress at the time of challenge and who were unable to envision some satisfactory resolution were prone to report symptoms to a greater extent than were individuals who felt there were few difficulties they could not handle.

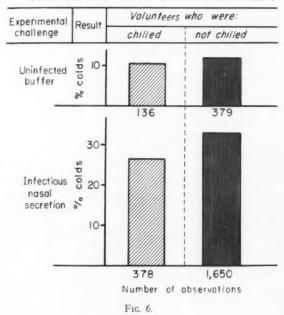
Variation also was found in the subjective evaluation of the severity of an experimental cold and the actual symptom score reported. Some persons were more prone to consider any abnormal symptoms as quite a severe cold, whereas others considered marked symptoms as only a mild cold. Thus, although the evidence for psychologic influence upon manifesting or reporting symptoms after experimental challenge seems clear, the virologic and immunologic factors obscured it to the extent that prediction of susceptibility or resistance on the basis of psychologic material alone was no better than chance.

Environmental and Physiologic Influences Upon Susceptibility:

Environmental Chilling. The effect of chilling volunteers upon their susceptibility to infection was examined in several ways. In some experiments, subjects in scant dress were kept in an environment of 60° F. with

80% relative humidity for four hours, which caused total body chilling. The effect of frigid air was tested by exposing warmly clothed volunteers to a temperature of 10° F. with 80% relative humidity for a period of two hours. Simultaneous control subjects were kept in comfortable dress at a temperature of 80° F. and 30% relative humidity. In each group, a proportion of the subjects who served as uninfected controls received only the saline solution used as diluent for the nasal secretion. The results of these experiments are summarized in figure 6, which includes additional observations on unchilled volunteers with the same result as in those who

CONTROLLED EFFECT OF CHILLING VOLUNTEERS



served as simultaneous controls in the chilling experiments. The data show two important features:

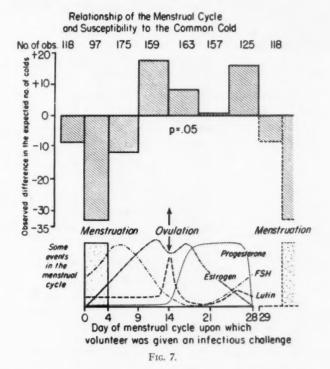
1. Among uninfected subjects, chilling did not activate latent viruses with the production of a clinical cold, since the observed frequency of colds after chilling was no greater than among unchilled persons.

Among subjects who received a uniform challenge, chilling did not increase the susceptibility to clinical infection, since the observed frequency of colds was slightly less than among unchilled subjects.

Physiologic Status of the Host. Fatigue resulting from exercise on a treadmill, or as the result of sleep deprivation for as long as 56 hours,

caused an insignificant increase in the frequency with which colds were observed to follow an infectious challenge.

Among females, susceptibility was significantly related to the menstrual cycle, as shown in figure 7. Attempts to initiate infection at the time of menstruation were relatively unsuccessful. After the cessation of menstruation, an increased susceptibility was observed, which reached a peak in the immediate preovulatory period. A second peak of high susceptibility appeared to occur in the immediate premenstrual phase. Girls who were challenged 29 days or more after the last menstrual period tended to be refractory, though menstrual flow had not begun.



Volunteers with hay fever during some season of the year, but not in the experimental period or with history of an ingestant allergy, who were experimentally infected tended to have a greater total symptom score than did other volunteers, and thus a significantly greater susceptibility by the criteria for an experimental cold. Previous tonsillectomy had no influence on susceptibility or symptoms, nor did the smoking history of the person.

Antibody Against the Common Cold: To determine whether the common cold viruses were antigenic, and whether they elicited an antibody re-

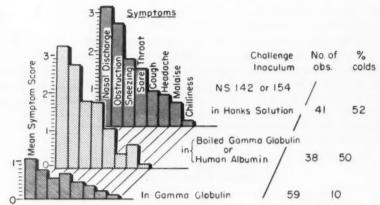
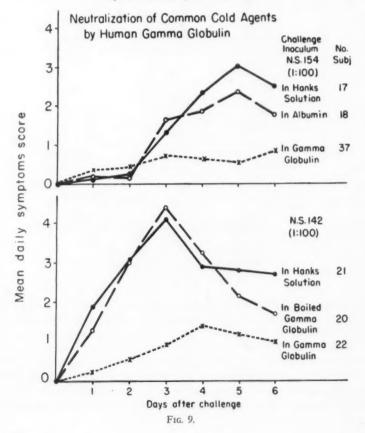


Fig. 8. Effect of preincubation of nasal secretion with pooled human gamma globulin upon its infectivity for volunteers.



sponse under conditions of natural infection, pooled human gamma globulin was tested for its capacity to neutralize the infectivity of the common cold agents in nasal secretions. As shown in figure 8, the prechallenge incubation of an infectious secretion for 30 minutes at 37° C. with Hanks' buffered saline solution did not change its capacity to cause a typical common cold, whereas all of the symptoms of infection were significantly suppressed by prechallenge incubation with gamma globulin. This protective effect was not present in human albumin of the same protein concentration or viscosity as the solution of gamma globulin. The protective component in gamma globulin was destroyed by boiling; and, since the material used was 97% gamma globulin by chemical and electrophoretic analysis, the data suggest

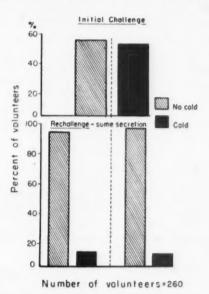
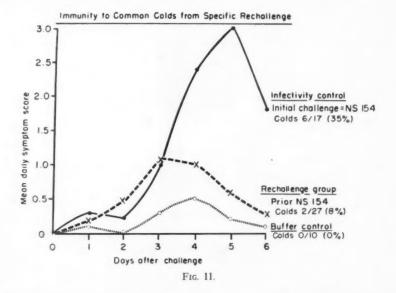


Fig. 10. The frequency of colds in volunteers upon two successive challenges with the same infectious nasal secretion.

that the protective effect was produced by a neutralizing antibody. As shown in figure 9, pooled human gamma globulin neutralized two different common cold secretions, one of which (N.S. 154) produced an illness with a long incubation period, and the other (N.S. 142) an illness with a short incubation period. The viruses present in the nasal secretions under study, or other viruses antigenically related to them, therefore appear to have caused infections among human beings within recent years.

To explore the possibility of a relationship between prior infection with known respiratory viruses and susceptibility or immunity to challenge with the common cold viruses, serum specimens from volunteers were tested for antibody against two strains of influenza A virus, two strains of influenza B virus, and adenoviruses. No relationship was shown. Both the number of persons with antibody and the mean complement-fixing antibody titer against these viruses were similar among persons who were experimentally susceptible or immune to the common cold. Serologic studies with several other viruses failed to show any cross-protection or relationship between them and the common cold agents.

Specific Immunity to Rechallenge: The question of wnether clinical infection would protect an individual against reinfection and, if so, the specificity of the response, was examined by rechallenging volunteers with the same or with a different infectious secretion. Among 260 volunteers who received the same infectious secretion on two different occasions, it



was observed, as shown in figure 10, that most of the subjects who were resistant to clinical illness in the first challenge were likewise immune upon rechallenge. Also, subjects who had a cold from the initial challenge showed the same degree of immunity to rechallenge as did those who were initially resistant. Volunteers who were challenged successively with two different secretions showed no comparable immunity; the frequency of colds in the second challenge was approximately the same as that observed in the initial challenge.

The immunity to rechallenge with the same secretion was not the result of decreased infectivity of the secretion. Volunteers who received an initial challenge simultaneously with others who were being rechallenged showed significantly more illness, whether measured by the number of colds or, as

shown in figure 11, the frequency of symptoms in the entire group. Among subjects who had received a prior challenge, fewer developed symptoms, and the symptoms were milder and subsided more quickly. This result was shown to be independent of the number of times a subject had participated in the experiments, and was related only to the prior administration of the same virus. The data closely resemble those observed after preincubation of virus with gamma globulin, shown in figure 9.

#### DISCUSSION

At the present time, the causative agents of the common cold appear to be several, if not a great many, different viruses. These viruses produce both clinical and subclinical infections in man and, from serologic studies, some may cause inapparent infections in animals. Each of the viruses can produce a variety of clinical syndromes, which are commonly classified under categories of common cold, undifferentiated upper respiratory infection, and "flu." The common cold viruses cause afebrile, acute coryza in the great majority of persons. With a tew exceptions, acute coryza in the great majority of persons. With a tew exceptions, acute coryza in the great majority of persons or well characterized. Influenza, coxsackie and adenoviruses may be considered at the other end of the spectrum of respiratory viral infections, in which the major clinical manifestations are fever, pharyngitis and lower respiratory symptoms, although a smaller number of patients have common coldlike illnesses. 12

The common cold viruses are present in infectious form in both the cells and the fluid of nasal secretions; the titer is sufficient to suggest that droplet spray could be an effective means of communicating infection. Person-to-person transfer, presumably by droplet spray, was observed to cause clinical illness in approximately 10% of persons exposed under experimental conditions, and in 17 to 55% among family members. In contrast to age, multiple colds within the family made little difference upon the secondary attack rate, which suggests that the infections were caused by the same virus. The viruses in the community at different times, however, appear to be immunologically different, and some seem to cause sharp waves of epidemic illness, whereas others are more endemic.

The cytopathogenic effect of infection upon the cells of the nasal mucosa in naturally acquired colds has been observed by Bryan and Bryan. 17, 18 The studies reported here included uninfected controls and subclinical infections, in addition to subjects with illness. The time of examination before and after challenge was uniform, and the microscopist did not know the nature of the challenge, whether the volunteer had symptoms, or the time when the specimen was taken. Under these conditions, stained smears had some degenerating cells before challenge which showed all of the features observed after infection. On the other hand, a cytopathogenic effect from infection was clearly demonstrable.

Observations in volunteers make it apparent that there is a distinction

between infection and illness. The latter is a variable complex related, perhaps, to the extent of viral infection, the psychologic attitudes and reactions of the host, his physiologic status at the time of contact with the virus, and probably even his hereditary endowment as judged by proneness to allergic rhinitis. The kind of symptoms by which the infection is manifest also is influenced by the host as well as the virus. Others have made similar observations in epidemiologic studies. <sup>19</sup>

The strong positive correlation between the usual number of colds per year by history and symptomatic reaction to an innocuous instillation appears to establish a wide range of difference in the proneness of persons to develop rhinorrhea or coryza. The data do not permit a conclusion as to whether physiologic or psychologic factors are dominant.<sup>20, 21</sup> On either basis, it is surprising that among the subjects who were hyperreactors to an uninfected solution, there was not greater susceptibility to clinical illness from a secretion containing an infectious agent. It may be that there is some sort of reciprocal function in the interplay of psychologic and physiologic factors; if one is heavily weighted, the other is obscured.

For centuries, men have associated the common cold with environmental chilling. Failure to confirm this relationship under conditions of experimental design in volunteers or in isolated arctic communities also has been experienced.<sup>3, 22, 23</sup> The present data seem adequate to conclude that the basis of the association is not the direct activation of latent viruses by physical cold or physiologic reaction to chilling, since these factors did not produce colds without infection. Furthermore, if the degree of infection was uniform, chilling prior to or at the time of challenge did not have an adverse effect upon the host. Although experimental conditions may not test the proper factors, it would appear that the prevalence of colds during the winter season and their occasional sudden increase following abrupt changes in atmospheric conditions must have some other basis than that of persons becoming chilled.

The relationship between susceptibility to viral infections and the menstrual cycle or pregnancy has been observed with other viral infections, 24 and previously reported by us with regard to the experimental common cold. 4 The present data confirm and extend the earlier observation with a larger group of subjects. In the earlier analysis, chilling was observed to exaggerate the susceptibility of females in the preovulatory period. A more significant factor, which was not so apparent in the earlier studies, is the decrease in susceptibility to infection during the period of menstrual flow. Although a clear relationship between ovarian or pituitary hormones and the differences in susceptibility is not apparent, it seems possible that the effect is related to changes in the surface mucosal epithelium under the control of the sex hormones.

There is no easy explanation for the epidemiologic and experimental observations that show insignificant immunity to the common cold.<sup>25, 26</sup>

The key to the problem is the elucidation of the number and specificity of the viruses, the rate and extent of the neutralizing antibody response, the availability of antibody to the cells of the nasal mucosa, and the duration of protection. Neutralizing antibody has been demonstrated in the serum <sup>5</sup> and nasal secretion, <sup>27</sup> and immunity to a specific rechallenge is as complete as that observed for influenza under natural conditions of infection. <sup>28</sup> The duration of immunity is not known, but it appears to remain through at least one respiratory disease season.

These observations require the postulate that each viral upper respiratory illness is a specific infection, and thus that the number of viruses responsible for these infections is very great. Other studies have shown that clinical and subclinical infections can occur in the presence of significant serum antibody titers, 6, 29, 30 but these are generally milder illnesses, and involve a small proportion of such people. From experimental data, the frequency of common colds is not well explained by recurrent symptomatic infections with the same virus. Under the concept that the common cold is caused by many specific agents, each of which elicits an adequate immune response, the likelihood of discovering a predominant common cold virus that maintains this role for a long time is quite unlikely. Also, if this is the case, the logistics for immunologic control of the common cold may be very difficult.

The results reported here and those obtained by others <sup>31, 32</sup> indicate that controlled studies in volunteers may be essential to obtain evidence bearing on certain important factors in susceptibility, illness, and immunity to common viral respiratory infections, and that such studies will be necessary in conjunction with the development of tissue culture methods which permit isolation and characterization of additional new viruses.

#### SUMMARY AND CONCLUSIONS

Studies in volunteers have shown that the common cold syndrome can be produced by uncharacterized filtrable agents in the nasal secretions of persons having a common cold. The experimental illness resembled that resulting from natural infection. The predominant features were afebrile coryza with increased nasal discharge and congestion, but different viruses produced a greater or less degree of noncoryzal pharyngitis, and occasionally a febrile respiratory infection. Subclinical infections were shown by observing the cytopathogenic effect of infection on the cells of the nasal mucosa. Common cold viruses were demonstrated both in the nasal epithelial cells and in the cell-free nasal secretion. The secretions from symptomatic donors usually contained more than 100 infectious doses per milliliter.

Certain persons who reported proneness to natural infections frequently developed coldlike symptoms from the instillation of a noninfectious salt solution, but they showed no greater susceptibility to infectious material than did other volunteers. A small group of persons were resistant to natural and experimental infections. Although psychologic factors were important in some respects, prediction of susceptibility from psychologic studies was not successful. Under experimental conditions, neither total body chilling nor frigid conditions induced spontaneous infections or increased susceptibility to experimental infection. Sleep deprivation and fatigue increased infectivity insignificantly. Girls showed significant differences in susceptibility in relation to different phases of the menstrual cycle.

Pooled human gamma globulin neutralized the infectivity of several viruses associated with natural common colds. Immunity to specific common cold viruses was shown by rechallenging volunteers with the same and different infectious nasal secretions. It is suggested that the common cold syndrome in man is caused by specific viral infections, each of which elicits an appropriate immune response.

#### ACKNOWLEDGMENT

We should like to acknowledge with thanks the help of the following persons who participated in some aspects of these studies: A. B. Boand, Ph.D., Gloria Cooper, B.A., Tohru Inouye, M.S., Betty Sullivan, Diane Trembly, M.D., Theodore Wakefield, M.D., and Frieda K. Webb, B.S.; and to express appreciation to the many students from the University of Illinois, Colleges of Medicine, Dentistry and Nursing; Cook County School of Nursing; Presbyterian-St. Luke's School of Nursing; Loyola Schools of Medicine and Dentistry; Chicago Medical School, and others who have participated as volunteer subjects.

#### SUMMARIO IN INTERLINGUA

Studios con voluntarios ha monstrate que le syndrome del catarrho commun pote esser producite per non-characterisate filtrabile agentes ab le secretiones nasal de personas afficite de un catarrho commun. Le morbo experimental resimilava le morbo que resulta de infection natural. Le aspectos predominante esseva coryza sin febre con augmento del secretion nasal e con congestion nasal, sed diverse typos de virus produceva un major o minor grado de pharyngitis noncoryzal e in certe casos un infection respiratori con febre. Infectiones subclinic esseva demonstrate per observar le effecto cytopathogene del infection in le cellulas del mucosa nasal. Viruses de catarrho commun esseva demonstrate tanto in le cellulas naso-epithelial e in le secretion nasal acellular. Usualmente le secretiones ab donatores symptomatic contineva plus que 100 doses infectiose per millilitro.

Certe subjectos qui reportava un predisposition a contraher infectiones naturalmente frequentemente disveloppava symptomas catarrhoide post le instillation de un non-infectiose solution salin, sed illes non monstrava un plus alte grado de susceptibilitate pro le material infectiose que le altere voluntarios. Un micre gruppo de subjectos esseva resistente a infectiones tanto natural como etiam experimental. Ben que factores psychologic esseva importante in certe respectos, il non esseva possibile predicer le susceptibilitate o non-susceptibilitate del subjectos super le base de studios psychologic. Sub le conditiones experimental usate, nulle infection spontanee e nulle augmento del susceptibilitate al infection experimental esseva producite per (1) le refrigidation del corpore total o (2) le exposition a conditiones de frigiditate. Le privation de somnio e fatiga augmentava le infectivitate de maniera non statisticamente significative. Femininas manifestava differentias significative in le grado del susceptibilitate in relation a differente phases del cyclo menstrual.

Globulina gamma human originari de un reservoir collective neutralisava le infectivitate de plures del viruses que es associate con catarrhos commun natural. Immunitate pro specific viruses de catarrho commun esseva demonstrate per reprovocar voluntarios con le mesme e con altere secretiones nasal. Es suggerite que le syndrome del catarrho commun in humanos es causate per specific infectiones virusal e que cata un de ille infectiones evoca un appropriate responsa immunologic.

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# METHYLTESTOSTERONE THERAPY FOR HEREDI-TARY EPISODIC EDEMA (HEREDITARY ANGIONEUROTIC EDEMA)\*

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HEREDITARY episodic edema is a rare disease, manifested by recurring attacks of spreading edema which appear rapidly, last only a few days, and leave the patient healthy between episodes. The hereditary pattern is that of a dominant genetic abnormality. The edema may involve the skin or the wall of the mouth, pharynx, larynx or gastrointestinal tract. Edema of the larynx constitutes a grave emergency which may cause death. The clinical features in two families studied personally and in others reported in the literature have previously been reviewed in detail.<sup>1</sup>

Although knowledge of the clinical manifestations, heredity and prognosis is adequate, the fundamental nature of the disease has not been revealed, nor has any effective treatment been found. Professor Sylvia Bensley, of our Department of Anatomy (Section of Histology), originally suggested that testosterone might prevent the attacks of edema in this disorder, possibly by antagonizing the effect of histamine. The work reported

in this paper appears to confirm the suggestion.

The disease is usually called hereditary angioneurotic edema, but a better name would be hereditary episodic edema. "Angioneurotic" means a neurosis involving blood vessels. Although formerly "neurosis" was used in the sense of nervous control, it is now used chiefly with reference to a group of mental illnesses. In the disease under discussion there is neither evidence of mental illness nor proof that the fundamental defect is related to the nervous control of blood vessels. Accordingly, the alternative title of hereditary episodic edema is suggested to emphasize the recurrent character of the edema (in contradistinction to another form of hereditary edema, Milroy's disease, which is chronic), and to remove the misleading word "angioneurotic."

## Метнор

Six patients from the same family (none siblings of any other) were given methyltestosterone, in the form either of buccal linguets or of tablets to be swallowed. The dose varied from 10 to 20 mg. daily of the linguets, and from 20 to 40 mg. daily of the tablets. Placebos identical with the tablets were used in three of the patients. Because of the possibility of

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laryngeal edema occurring during the placebo-controlled trial, it was felt to be unethical to conduct a strict double-blind study. Accordingly, the patients were told they would be given either placebos or active tablets, but until the end of the study neither they nor I knew the order in which the tablets had been taken. For 10 consecutive periods of 25 days each, they took either methyltestosterone tablets to swallow or placebos. The dose was 20 mg. twice a day.

#### CASE REPORTS

Case 1. A 30 year old man has had attacks of abdominal pain and edema of the body surfaces every few weeks since the age of seven.\(^1\) One year before beginning to take methyltestosterone he had an attack of laryngeal edema which necessitated an emergency tracheotomy. During this year the episodes of pain and superficial swelling were causing him to miss so much time at work that he was in danger of losing his job. Attempts to prevent attacks with Pyribenzamine had failed; corti-

Table 1
Effect of Methyltestosterone on Frequency of Attacks in Case 1

Dates	Methyltestosterone	Number of Attacks		
Dates	(mg. daily)	Abdominal	Superficial Swelling	
Nov. 1952-Aug. 1953	0	12	6	
Sept. 1953-May 24, 1954	20	0	0	
May 24-26, 1954*	0	0	1	
May 27-July 1954	10	0	0	
AugSept. 17, 1954†	5	1	0	
Sept. 18-Oct. 1954	10	0	0	
NovDec. 1954	20	0	0	

\* Patient went fishing for a few days and forgot to take the linguets. After he had missed two days of medication, his hand became edematous.

† To reduce the cost of the medication, patient decreased the dose to 5 mg. daily and, after six weeks, had an abdominal attack.

sone, the intravenous administration of ACTH, and adrenalin had failed to arrest attacks of edema once they had begun. Since the end of 1952 the patient has kept a careful written record of each attack, and has been seen by me during many of them. Table 1 summarizes the experience during the first two years of study and shows the effects of methyltestosterone.

The experience during this two-year period indicated that, as long as the patient took a 10-mg. linguet (or more) daily, the attacks did not occur. During 14 months on this medication he had no attacks, whereas in the 11 months during which he took smaller doses or none at all he had 20 attacks. Following this, a placebo-controlled trial was carried out. Table 2 contains the results for this patient as well as for cases 2 and 3. During the five periods in which he took placebos there were five abdominal attacks and eight episodes of superficial edema, whereas he was free of attacks while taking 40 mg. of methyltestosterone daily during the balance of the trial period.

Since this trial in 1955 the patient has taken methyltestosterone linguets continuously except when the effects of other drugs were being observed. Over the

Table 2
Placebo-Controlled Trials of Methyltestosterone

	Number of A	Abdominal Attacks	Number of S	uperficial Swellings
	Placebo	Methyltestosterone	Placebo	Methyltestosteron
Case 1	5	0	8	0
Case 2	4	0	2	1*
Case 3†	2	0	4	0

<sup>\*</sup> One episode of superficial edema began four days after the start of a period of methyltestosterone tablets.

† On one occasion the superficial swelling and abdominal pain occurred simultaneously.

four-year period he has had a few attacks when the dose of methyltestosterone was lowered or the drug omitted. Edema of the face and pharynx occurred several weeks after the dose of methyltestosterone linguets had been reduced from 10 mg. to 7.5 mg. daily. Edema of one foot followed a trial of methylandrostenediol, 20 mg. daily for 11 weeks. Three abdominal attacks took place, two of them after methyltestosterone had been discontinued for one week to study the effect of intravenously administered testosterone glucoside. The first time he was given 120 mg. in 48 hours, and the second time, 250 mg. in 36 hours. No benefit was observed on either occasion. The third abdominal attack took place while he was taking a 10-mg. linguet of methyltestosterone daily. It lasted for more than a week, being of longer duration than any of his previous episodes. Radiologically there was evidence of ileus. The diagnosis was considered to be bowel obstruction from a cause other than hereditary episodic edema.

In summary, one can say that during six years of observation this patient has had no attacks of superficial edema while taking methyltestosterone in a dose which is adequate for him, namely, one 10-mg. linguet daily. One episode of abdominal pain occurred, but it was attributed to a cause other than his hereditary edema. The only side-effect of the treatment has been a moderate degree of bilateral gynecomastia. A sperm count and microscopic study of the morphology of the spermatozoa done after the first year of treatment were normal. Since then he has fathered one healthy child.

Case 2. A 32 year old man has had attacks of abdominal pain and superficial swellings since the age of nine. They have come at intervals of about one month. Since early 1957 the patient has kept detailed notes of his symptoms. Table 3 summarizes the effect of methyltestosterone treatment since then, except for a period of

 $\label{table 3} {\it Table 3}$  Effect of Methyltestosterone on Frequency of Attacks in Case 2

Dates	Methyltestosterone	Number of Attacks		
Dates	(mg. daily)	Abdominal	Superficial Swelling	
JanMay 16, 1957	0	3	3	
May 17-28, 1957	10	1	0	
May 29-Aug. 18, 1957	20	0	0	
Apr. 30-June 8, 1958	20	1	1	
June 9-Sept. 23, 1958	40	0	0	
Sept. 24-Nov. 26, 1958	30	0	0	

placebo-controlled medication using the same dose as in case 1. The results of the placebo-controlled trial are recorded in table 2.

This patient appears to require a larger dose of methyltestosterone than does the first patient. While receiving 30 mg, or more in tablet form daily he had no attacks in more than six months, whereas with no medication, or with as much as 20 mg. of the linguets daily, he had five abdominal attacks and four swellings in a little less than nine months.

During the placebo-controlled trial (table 3) the patient had a single episode of superficial edema while taking methyltestosterone. This episode began four days after changing from placebo to methyltestosterone tablets. The attack may have come in spite of the methyltestosterone, or it might indicate that he required more than four days of treatment before attacks were prevented.

No side-effects have been observed in this case.

Case 3. A 21 year old male has had attacks of either "swellings" or "pains" every two to four weeks since the age of 10. He came under observation in December, 1956, and began to take one 10-mg. linguet of methyltestosterone daily at that time. During the next nine months he had only one attack, which came the day after he had taken only half a linguet (5 mg.). In this episode his right foot, left hand and left forearm became swollen. The results of a placebo-controlled study similar to the other two are summarized in table 2.

During the time the patient took placebos, five separate episodes occurred, whereas he was free of them while taking methyltestosterone tablets, 40 mg. daily. He has been followed for six months since the placebo-controlled trial. He takes a 10-mg. linguet daily and has had no attacks. The only side-effect has been a worsening of his chronic acne.

Case 4. A 54 year old female began to have attacks of abdominal pain and vomiting at age 16, recurring every two or three weeks. At age 22 the swellings began, but there have been no attacks of superficial edema in the last few years. She has been under the care of Dr. D. R. Rudd, of Moose Jaw, Saskatchewan, who has kindly notified me of her progress. From August, 1956, until February, 1957, she had six episodes of abdominal colic, during two of which she was admitted to hospital and given fluids intravenously. In February, 1957, she began to take methyltestosterone linguets, 10 mg. daily. Because of a slight growth of hair on the upper lip and the appearance of a few pimples, the dose was reduced to 5 mg. in September, 1957. Since then these side-effects have diminished. From February, 1957, until the last report (December, 1958), she has had no further attacks.

In this case there have been no attacks while the patient was taking either 5 or

10 mg. of methyltestosterone daily.

Case 5. A 66 year old male, father of case 1, in recent years has had infrequent attacks of superficial edema or abdominal pain. During the four years preceding methyltestosterone therapy he had four episodes of abdominal pain and two attacks of edema, both affecting the face and pharynx. He has taken one 10-mg. linguet of methyltestosterone daily for two years and has had no attacks. The infrequency of attacks, and the fact that in this disease patients may become free of episodic edema in later life, make it impossible to draw conclusions about the effectiveness of methyltestosterone in this case.

Case 6. A 27 year old female has had attacks of abdominal pain and superficial swellings since age 17. The episodes of pain, which are more frequent than the swellings, come about once a month. Both her father and her sister died of laryngeal edema, the latter at age 25. Dr. D. McNeill, of Calgary, Alberta, kindly advises that she was unable to take testosterone compounds for more than a few

weeks because of the appearance of acne.

#### DISCUSSION

In these patients, relatively small doses of methyltestosterone prevented attacks of hereditary episodic edema. The best evidence is to be found in table 2. During the time these three patients were taking methyltestosterone, one attack characteristic of the disease was noted. During the same length of time in which placebos were ingested, 24 separate attacks occurred. (Probability is less than 0.01.) The single attack which occurred during treatment with methyltestosterone came four days after switching from the placebo to the androgen. The episode may have appeared before the androgen had had time to be effective.

It is interesting to speculate about the action of methyltestosterone in these patients. Professor Sylvia Bensley has observed that testosterone protects male guinea pigs from some of the effects of histamine (unpublished observations). Whether excessive histamine is liberated in the tissues of patients with hereditary episodic edema and plays a part in the attacks is not known. The possibility exists that patients with hereditary episodic edema produce an excessive amount of histamine and hyaluronidase in response to slight injury to tissue. Or these patients may lack biochemical antagonists of histamine and hyaluronidase. Hamilton <sup>2</sup> found that testosterone propionate administered to ovariectomized hamsters increased the thickness of the collagenous fibers in the skin within five days. This observation suggests an explanation for the effect of testosterone in these patients. Under treatment with methyltestosterone, the thickness of collagen in and below the skin, as well as in the wall of the intestine, may increase enough to prevent the accumulation and spread of edema fluid.

No serious toxic effects of methyltestosterone have been observed in this group of patients. The dose by mouth (i.e., swallowed) recommended for replacement therapy in hypogonadism is 20 to 50 mg. per day. Linguets are reported to be more effective than tablets, the dose of linguets for replacement therapy being 5 to 30 mg. per day.<sup>3</sup> Thus, in this study the doses used were within the range recommended for replacement therapy. We were unable to use linguets in placebo-controlled trials because the distinctive taste of methyltestosterone linguets could not be reproduced in a placebo. A few minor side-effects were noted in this small group of patients, namely, acne, gynecomastia and facial hirsutism. Jaundice, which has been reported <sup>4, 5</sup> as a rare toxic effect of methyltestosterone, did not occur. Doses of 75 to 200 mg. of methyltestosterone daily have been observed to depress the sperm count in the majority of human subjects within a few weeks.<sup>6, 7</sup> The effect is slowly reversible. Whether smaller doses depress spermatogenesis in some subjects is not known.

One wonders whether methyltestosterone might prevent attacks of angioneurotic edema of the nonhereditary type. Such patients rarely have attacks that are sufficiently frequent and regular to make trials with drugs feasible. So far I have not seen a suitable patient. Similarly, it might be thought that methyltestosterone would be of benefit in treating chronic urticaria. Five patients with chronic urticaria were given doses of methyltestosterone tablets to a maximum of 60 mg. daily for periods of up to several months, without success. The explanation may lie in the effect of testosterone on collagen tissue.<sup>2</sup> Urticaria is a lesion of the more superficial portion of the skin, where collagen tissue is less abundant.

#### SUMMARY

1. The administration of methyltestosterone in small doses taken daily appeared to prevent attacks of edema in four members of a family suffering from hereditary episodic edema. In three cases, attacks reappeared during the use of placebos.

2. Possible roles of testosterone, histamine and hyaluronidase in this disease have been suggested.

3. The term "hereditary episodic edema" is recommended in preference to the usual but less accurate name, "hereditary angioneurotic edema."

#### ACKNOWLEDGMENT

Dr. Walter Murphy, Medical Director of the Ciba Company of Canada, kindly supplied the methyltestosterone tablets and placebos, as well as testosterone glucoside for use intravenously.

#### SUMMARIO IN INTERLINGUA

Iste morbo rar, que affice ambe sexos, se transmitte geneticamente con le configuration mendelian de un anormalitate dominante. Le characteristica essential del condition es es le apparition e propagation rapide de un edema que interessa le pelle o le pariete del bucca, del pharynge, del larynge, o del vias gastrointestinal. Le attaccos de edema occurre usualmente a intervallos de plure septimanas o menses. Illos dura plure dies, e alora illos dispare, e le patiente se trova ben usque al proxime attacco. Quando le intestino es afficite, sever grados de un colicoide dolor abdominal es presente. Edema del larynge pote devenir mortal.

Le designation usual, "angioneurotic edema hereditari," es deceptive. Neurose non es un aspecto del morbo, e il existe nulle prova que le disordine fundamental es un defecto del governamento nervose del vasos de sanguine. Le novemente proponite designation, "episodic edema hereditari," sublinea le character recurrente del edema e elimina le suggestiones inherente in le termino "angioneurotic."

Le administration de methyltestosterona in le forma de linguettas o tablettas se provava capace a prevenir le attaccos in quatro membros de un afficite familia. In tres casos le attaccos repareva durante le uso de placebos. Le dosage diurne esseva micre, equivalente al dosage usate in therapia de reimplaciamento in conditiones in que le production de androgenos es deficiente.

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## CORONARY THROMBOSIS, CEREBRAL VASCULAR ACCIDENT AND PULMONARY EMBOLISM IN LEPROSY\*

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In July, 1957, the author reported the incidence of fatal coronary thrombosis (myocardial infarction, coronary occlusion, "coronary," "heart attack") in tuberculous white men of 40 years and above to be significantly lower than in a corresponding group without a history of tuberculosis. Attention was called to earlier reports on the low incidence of pulmonary embolism in tuberculous patients. The theory was advanced that tuberculous infection "provokes some response in the body which has a protective action against coronary thrombosis and thrombo-embolic phenomena in general." A circulating anticoagulant was suggested.

A natural sequel to this work would be a similar study in a comparable disease state. Since there are many points of similarity between tuberculosis and leprosy, a study of the incidence of the common diseases associated with vascular clotting in the latter has been carried out. This report is therefore concerned with the incidence of fatal coronary thrombosis, cerebral vascular accident and pulmonary embolism in people with leprosy. The material for the investigation was obtained from the U. S. Public Health Service Hospital, Carville, Louisiana, the national leprosarium. The following tabulations give some general information about deaths at Carville.

Massive pulmonary embolism occurred four times in the 519 autopsied cases, for an incidence of 0.77%. This is a remarkably low number, considering that a commonly accepted figure for the incidence of massive pul-

monary embolism in routine autopsies is 4%.2

Deaths of white males aged 40 and above were analyzed with respect to the incidence of coronary thrombosis and cerebral vascular accident. Subjects dying of leprosy or its complications, or tuberculosis or its complications, were excluded from the study (the latter because this disease was a common cause of death in leprosy prior to the advent of effective antituberculosis and leprosy drugs). These exclusions were made to overcome the objection that leprosy may kill before other diseases can develop. One hundred one deaths were found in this category (white, male, aged 40 and above). Ages ranged from 40 years through 92 years, with an average age of 63.5 years. There were nine deaths due to coronary thrombosis (as defined in this paper) and five deaths due to cerebral vascular accident.

<sup>\*</sup> Received for publication November 23, 1959.
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TABLE 1

U. S. Public Health Service Hospital, Carville, Louisiana Statistics on Deaths from February, 1921, to July 7, 1959

Total deaths at this hospital	685	
Deaths of patients while in the Orleans Hospital and on lear		
	Total deaths	701
Total number of autopsies out	of the 701	519
Sex of the 701 deaths		
Male Female	516 185	
Sex of the 519 autopsy cases		
Male Female	386 133	
Race of the 701 death cases:		
White Negro Mongolian Other	570 93 30 8	
Race of the 519 autopsy cases		
White Negro Mongolian Other	403 81 27 8	
Average age of the 701 death of	ases	50.1 years
Average age of the 519 autopsy	cases	51.3 years
Average age per five-year perio	ds:	
Years	No. of Deaths	Average Age
1921-1925 1926-1930	63 97	44.8 47.5

1931-1935	113	45.2
1936-1940	154	48.9
1941-1945	130	51.5
1946-1950	63	54.7
1951-1955	51	61.1
1955-mid-1959	30	60.5

Deaths according to certain causes in the 701 total deaths:

	Number	% of Total Deaths
Coronary thrombosis	17	2.43%
Cerebral vascular accident	11	1.57%
Pulmonary embolism	4	0.57%
Malignant disease	49	6.99%

Twenty deaths were due to malignant disease. These data are summarized as follows:

TABLE 2

Leprosy Cases, White, Male, Aged 40 and Above, Dying of Causes other than Leprosy or Its Complications

Average age, 63.5 yea	rs
Total number of cases	101
Coronary thrombosis	9 (9%)
Cerebral vascular acci	dent 5 (5%)
Malignant diseases	20 (20%)

As is readily apparent, the number of deaths from coronary thrombosis and cerebral vascular accident is low. A control group to compare with this leprosy group, however, is not easy to obtain. It should be pointed out that the situation at Carville is unique in several important respects that are difficult if not impossible to match. First, the majority of the inhabitants of this unusual community who die come to autopsy, as can be seen from table 1. Second, excellent hospital facilities are readily and quickly available to all. This combination insures a degree of accuracy of diagnosis which probably cannot be matched in any other community. Carville is a "community" as well as a hospital, since a large number of patients who are admitted live out their lives here. It might seem that records from a general hospital would provide a good control group, but deaths occurring in a general hospital do not necessarily reflect the incidence of deaths from various diseases in the city in which it is located. For instance, many sudden deaths from heart attacks and strokes may occur before there is time for the patients to reach a hospital. Also, in the earlier years covered by this study, which extends from 1921 into 1959, it may be assumed that the bulk of medical deaths in a city occurred at home and not in a hospital. Death certificates provide a poor control group, because the inadequacies of diagnoses appearing on unselected death certificates in the 1920's and 1930's as far as statistical study is concerned are obvious on inspection. The problem of finding a representative segment of the general population to compare with the unique population at Carville is at least partially met by using physicians as controls. It has been the practice for many years (now, unfortunately, abandoned) to note the age and cause of death of deceased physicians in the obituary columns of the Journal of the American Medical Association. sex of the physician is usually obvious from the name, and the great majority are known to be white. The accuracy of the diagnoses appearing in the Journal seems to be of a much higher order than that of those taken at random from death certificates; this is especially true of the earlier years encompassed in this study. Therefore, people with leprosy have been compared with physicians. There is no convincing evidence that the incidence of deaths from heart attacks and strokes in physicians is a great deal different from that in the general population. (It is now recognized that about one third of white men above the age of 40 who die, accidental death excluded, die of a heart attack. It will be seen that this figure approximates the incidence of death due to heart attacks in the physician control group used in this study.)

The control group of deceased physicians was obtained by matching age for age at random in the obituary columns of the *Journal* and noting the cause of death. If a cause of death appeared which could or could not refer to coronary thrombosis, it was passed over. Cases were also matched as to the year in which the death occurred, an important consideration. Deaths due to accidents were excluded because the risk of accidental death at Carville

is practically nil. Data concerning the control group are summarized as follows:

TABLE 3

Physicians (Presumably White), Male, Aged 40 and Above, Dying of Causes other than Accident

Average age, 63.5 years		
Total number of cases	101	
Coronary thrombosis	29	(29%)
Cerebral vascular accident	17	(17%)
Malignant disease	9	(9%)

Combining tables 2 and 3 gives the following results:

TABLE 4

		_			
	Total Deaths	Coronary Thrombosis	C.V.A.	Malignant Disease	
People with leprosy	101	9 (9%)	5 (5%)	20 (20%)	
Physicians	101	29 (29%)	17 (17%)	9 (9%)	

## DISCUSSION

Before this discussion begins it is necessary to point out that, contrary to general belief, most deaths due to cerebral vascular accident are due to thrombosis rather than to hemorrhage.<sup>8</sup>

There are several ways to explain the apparent low incidence of deaths from heart attacks and strokes in this unusual population (at Carville). First, leprosy may in some way increase the incidence of deaths from all other categories, thereby, in a study such as this, diminishing the percentage of heart attack and stroke deaths. (It will be noted that diseases recognized as complications of leprosy have been omitted.) Since we do not know the cause of many important diseases, especially cancer, it cannot be said with certainty that this has not occurred. (It should be noted here that coronary thrombosis was the cause of death in only 17 of the 701 total deaths shown in table 1. Malignant disease was the cause of death in 49 cases. Ordinarily, in an adult population, predominantly white and predominantly male, there will be about two deaths due to heart attack for every death due to cancer.4 A striking reversal of the distribution of deaths between myocardial infarction and cancer is shown by these figures. Either cancer deaths are increased, or coronary deaths are decreased, and the latter seems most likely.)

If we assume that the reduction in incidence of coronary thrombosis and cerebral vascular accident is real, several possible explanations must be examined.

It may be said that leprosy attacks a type of person not prone to strokes or heart attacks, and this cannot be disproved.

There is no denying that these unfortunate people live a totally sheltered

life. With no wish to minimize the tragic effects of this ancient disease, it should nevertheless be pointed out that the majority of patients at Carville are ambulatory: many work as orderlies, maintenance men, etc., and there is physical recreation—Carville boasts a golf-course, a baseball diamond, and a baseball team which plays in a league in the area. There are dances and other social activities. Passes are allowed, and many shop in Baton Rouge, which is about 30 miles away. Smoking habits are not remarkable. What effect this life may have on the incidence of thrombotic disease is purely speculative, but of course it cannot be denied that it may have an effect. They may not have the "stresses and strains of modern living," but no one would deny their own peculiar stresses. Two suicides occurred in these 101 cases.

The matter of diet and nutrition must be considered. In general, patients are well nourished. The diet is not remarkable; certainly there is no limitation of fat in the diet. (It should be pointed out here that there is no tendency to low cholesterol blood levels in this community; in fact, the opposite appears to be the case.<sup>5</sup> This is in accord with a recent report from India.<sup>6</sup> It is interesting to note that the same trend was observed in tuberculosis, except, of course, in terminal cases.)

A possible explanation that deserves close attention is suggested by the low incidence of pulmonary embolism, which is about a fourth or a fifth of what could ordinarily be expected. (Atherosclerosis per se at Carville appears to be neither less nor more prevalent than in the general population.) In itself, this suggests an in vivo hypocoagulable state of the blood in leprosy. (There have been no intensive studies of blood coagulation in this disease, since hemorrhagic complications do not occur.)

A rather constant and striking feature of the blood in leprosy is an elevation of the serum globulin, usually with a lowered serum albumin.<sup>5</sup> An intriguing thought is that these changes may in some way inhibit vascular clotting. The same changes appear regularly in tuberculosis, where a lowered incidence of coronary thrombosis and pulmonary embolism has been reported, and in cirrhosis of the liver, where a low incidence of pulmonary embolism and myocardial infarction has been reported.<sup>1, 7, 8, 9, 10</sup> (In the latter disease of course specific clotting factors are frequently diminished.) In this connection, it is interesting to note that in Africa and Asia where coronary disease has been reported to be rare, serum globulins in the native populations frequently tend to be elevated.<sup>11</sup> This has been explained either as a racial characteristic, or as due to frequent contact with a variety of infections occurring in these areas.

Since newer knowledge of the fibrinolytic system has been accumulating, it is not too fanciful to speculate that this system is everyone's protection against vascular clotting. It has already been reported that coronary thrombosis has occurred where fibrinolytic activity is low.<sup>12</sup> In certain situations or groups it may be anticipated that fibrinolytic activity will be

higher than average, and in this situation it may be expected that diseases associated with blood clotting may be lower in incidence than in the general population. (Some direct evidence exists that increased or abnormal serum globulins may interfere with coagulation.\(^{18}\) This may come about by complexing of the abnormal globulin with clotting factors. Increased fibrinolytic activity has also been found in some cases with increased globulins.\(^{18}\) Perhaps this is the situation in leprosy and tuberculosis, and possibly in other diseases. At least the possibility is worthy of intensive study.

If, indeed, leprosy and tuberculosis "provoke a response in the body which has a protective action against coronary thrombosis and thromboembolic phenomena in general," the door is open to some form of immunization against these diseases.

# SUMMARY

Evidence is presented that the incidence of fatal heart attacks, strokes and pulmonary embolism in people afflicted with leprosy is a great deal less than could ordinarily be expected. It is postulated that leprosy, like tuberculosis, provokes a response in the body which has a protective action against these diseases. It is suggested that this is associated with an in vivo hypocoagulable state of the blood, mediated through an increase in the plasma globulins. This may be brought about by complexing of the unusual globulins with clotting factors, or by increased fibrinolytic activity, or both. If the concepts developed here prove to be correct, then the basic information necessary for the development of an immunization against thrombosis is provided.

#### ADDENDUM

In a prospective study of life insurance policy holders with apparently healed tuberculosis, 23 deaths due to circulatory diseases were found in standard cases where 46.88 were expected or one-half the expected number. 14 The difference was not thought to be due to stricter underwriting in the tuberculosis cases, and the diagnoses were positively made, not merely on x-ray films alone. 15

#### ACKNOWLEDGMENT

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#### SUMMARIO IN INTERLINGUA

In un previe publication, le autor presentava materiales indicante que le incidentia de mortal thrombose coronari ("attacco cardiac") in mascule tuberculoticos de racia blanc es significativemente plus basse que in correspondente gruppos de subjectos sin antecedentes de tuberculose. Le presente reporto es concernite con le incidentia, in patientes con lepra, de certe morbos que es associate con coagulos vascular, thrombose coronari, accidente cerebro-vascular, e embolismo pulmonar. Le datos pro le investigation esseva obtenite ab le Hospital Carville. Louisiana, del statounitese Servicio de

Sanitate Public (i.e. le Leprosario National). Un analyse del 701 mortes (con 519 necropsias) que ha occurrite a iste institution depost su establimento in 1921, thrombose coronari esseva trovate 17 vices, accidente cerebro-vascular 11 vices, embolismo pulmonar quatro vices, e cancere 49 vices. Massive embolismo pulmonar es usualmente incontrate in circa 4% del necropsias routinari. In le presente serie de 519 necropsias, illo esseva incontrate solmente quatro vices, i.e. le incidentia esseva 0,77%. In un population predominantemente de racia blanc e de sexo mascule como le presente, il ha ordinarimente duo mortes per attacco cardiac pro omne un morte per cancere. In le presente serie de casos le lepra, un frappante reversion de iste proportion es notate: Il habeva 49 mortes per cancere sed solmente 17 per attacco cardiac.

Esseva analysate additionalmente le 101 mortes in le presente serie in le quales le etate del patiente esseva 40 annos o plus. Le datos esseva comparate con illos de un analyse del mortes de medicos (presumitemente de racia blanc) qui moriva al mesme etates e in le mesme annos. Inter le casos con lepra, novem mortes (9%) esseva causate per thrombose coronari, sed le correspondente cifra pro le medicos del gruppo de controlo esseva 29 (29%). In le gruppo con lepra, accidentes cerebrovascular occurreva cinque vices (5%), durante que inter le medicos, 17 del mortes (17%) esseva causate per apoplexia cerebral. In le gruppo con lepra, malignitates causava 20 mortes (20%), in le medicos novem (9%).

Pro explicar le basse incidentia de thrombose coronari, de accidentes cerebrovascular, e de embolismo pulmonar in le population del Hospital Carville, le autor suggere le existentia de un stato de hypocoagulabilitate in vivo in le sanguine de patientes de lepra. Es etiam suggerite que isto es possibilemente mediate per un augmento del globulinas de plasma in iste morbo. Un tal catena de causa e effecto es forsan le consequentia del complexation de globulinas inusual con factores de coagulation o un augmento del activitate fibrinolytic o un combination de ambe istos. Si iste conceptiones se prova correcte, le base theoric es establite pro le disveloppamento de un methodo de immunisation contra thrombose.

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# FEVER IN MALIGNANT NEOPLASTIC DISEASE: A CONTROLLED STUDY OF TETRACYCLINE THERAPY \*

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#### INTRODUCTION

FEVER, in the absence of demonstrable infection, occurs frequently in patients with malignant neoplastic disease. Its pathogenesis is obscure. Occult bacterial infection 1, 2, 3 has not been excluded as a cause of such fever. While the availability of antibiotics has reduced morbidity and possibly prolonged survival in patients with malignant neoplastic disease, the decision as to whether they should be used in patients with fever without demonstrable infection remains a difficult and controversial one. Such fever frequently disappears with antibiotic therapy. 1, 3 but this may be a function of the natural duration of the fever, rather than a therapeutic response.4 Moreover, antibiotic administration, particularly to patients with depressed host defense, is not without risk. Bacterial infections, usually caused by resistant organisms, occur not infrequently in such circumstances, 1, 4, 5, 6

We have compared tetracycline and placebo therapy in episodes of fever of undetermined etiology in a heterogeneous group of patients with malignant neoplastic disease: (1) to test the hypothesis that such fever is due to occult bacterial infection; and (2) to investigate the potential benefits or hazards of short-term tetracycline therapy in patients with decreased host resistance.

#### MATERIALS AND METHODS

Patients with a febrile episode and no demonstrable infection were treated for two weeks with either tetracycline or placebo, whether fever persisted or disappeared. A coded technic was used, with only the statistician and the pharmacist aware of the identity of the particular drug in use. All patients hospitalized on the Chemotherapy Service of the National Cancer Institute between April 1, 1958, and March 1, 1959, were eligible for the study. A febrile episode was defined as: any rectal temperature in excess of 39.5° C., rectal temperature in excess of 38.5° C. on

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two of three successive days, or rectal temperature in excess of 38.0° C. for five of seven successive days. A febrile episode was considered to have terminated on the last day of fever followed by three afebrile days. Rectal temperatures were recorded on all hospitalized patients four times daily, and every four hours when fever was present. Fever within 24 hours following transfusion was not included.

Overt infection was considered to be excluded if no symptoms or signs of such infection were present (with the exception of fever per se), a chest x-ray and a blood culture were negative, and a midstream voided urine culture had a colony count of less than 100,000 organisms per cubic centimeter. Patients frequently received tetracycline or placebo before the results of the urine or blood cultures were known, and in two instances positive urine cultures were obtained in the absence of symptoms or signs suggesting urinary tract infection. These patients were removed from the study and are not included in the results.

Patients without demonstrable infection who met the above criteria for a febrile episode were immediately entered in the study. Only one febrile episode in each patient was studied, with the exception of two children with acute leukemia, in whom two febrile episodes were studied, and who had a complete hematologic remission between febrile episodes. The physician responsible for the patient's care in consultation with one of the authors (D. R. B.) had the option of excluding a patient from the study if, in his judgment, the possibility of septicemia was such as to demand antibiotic therapy prior to learning the results of the blood culture. This decision was made in six patients, four of whom in fact had positive blood cultures.

The patients were randomly allocated to tetracycline or placebo therapy. The mechanics of the randomization were such as to assure equal or nearly equal distribution of the two treatment programs within the following categories: the three types of onset of fever previously noted; and the type of disease: (1) acute leukemia in patients under age 15; (2) acute leukemia in patients age 15 and over: (3) Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, multiple myeloma and the chronic leukemias; (4) all other malignant neoplasms.

Tetracycline was given orally four times a day at a dose of 40 mg./kg./day (not to exceed 2 gm./day). One patient who received tetracycline was receiving corticosteroid therapy at the start of the study, and corticosteroid therapy was initiated in another patient during the study. In the placebo group, no patients were on corticosteroids at the start of the study, and in one patient corticosteroid therapy was initiated during the study.

Cultures of the pharynx, stool, blood and urine for bacteriologic and viral studies were obtained and performed as in a previous report before starting experimental therapy. Cultures of the pharynx and stool were repeated on the seventh day of therapy, three days after stopping the drug,

and two weeks after stopping the drug. A urine culture was repeated after the drug was discontinued. If fever persisted, blood cultures were repeated at a maximal interval of three days.

The rectal mucosa was swabbed through a sterile anoscope with a cotton-tipped applicator which was immediately placed in 2 ml. of trypticase soy broth. The following media were inoculated from the swab: cooked meat,\* selected lactobacillus medium <sup>7</sup> and tetrathionate broth; \* phenylethyl alcohol medium (PAM†) with blood, mannitol salt cetrimide, MacConkey's,\* desoxycholate citrate,\* modified Sabouraud's \* and SS agar plate.\* After one day of incubation, growth on tetrathionate broth \* was subcultured to MacConkey's and SS agar plates. Cooked meat was checked by Gram's stain and subcultured to aerobic and anaerobic blood and PAM agar plates on the first day. Radial streak plate subcultures were made from blood and PAM agar plates on the second day. From this growth, enterobacteria were identified by appropriate stains and subcultures. Streptococcus isolates were subcultured to bile aesculin agar slants \* for enterococcus identification.

The pharynx was swabbed with a dry cotton applicator which was immediately placed in 0.5 ml. of trypticase soy broth. Thioglycolate broth, blood agar, PAM and Sabouraud's agar plates were inoculated and incubated aerobically at 37° C. for two days or longer, and Gram's stain smears prepared from all media. Appropriate subcultures on radial blood agar plates were made by carefully picking colonies. These were examined with Gram's stain. Neisseria species were identified by sugar reactions when the colony morphology was doubtful.

Fungi from either pharynx or stool were identified by morphology on corn meal agar and rice-tween agar of Taschdjeau s and by carbohydrate fermentation reactions. Staphylococci were identified by their pigmentation, hemolysis, mannitol fermentation and coagulase activity. Culture plates with no growth were incubated for one week before being discarded.

A prior study of a similar group of patients indicated that Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, proteus, klebsiella and streptococci accounted for over 90% of bacterial infections. If we assumed that the same spectrum of microörganisms is responsible for occult bacterial infection, an antibiotic with a broad antibacterial spectrum was indicated. Furthermore, we desired an antibiotic that was effective when given orally. Tetracycline, oxytetracycline and chloramphenicol were considered. We reviewed the disc sensitivities of organisms responsible for infections during the preceding six months. By disc sensitivity, chloramphenicol was moderately superior to tetracycline for use in staphylococcus and proteus infections. Oxytetracycline was more effective than tetra-

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TABLE 1
Febrile Episodes Studied

Disease	Tetracycline	Placebo
Acute lymphoblastic leukemia	11	10
Acute myeloblastic leukemia	3	2
Hodgkin's disease	4	2
Reticulum cell sarcoma	2	0
Multiple myeloma	1	. 2
Rhabdomyosarcoma	1 '	1
Choriocarcinoma	0	1
Fibrosarcoma	1	0
Malignant melanoma	1	2
	Mildring	reman.
Total	24	20

cycline for pseudomonas, but less effective for staphylococci. Because chloramphenicol was not greatly superior and may produce bone marrow depression, it was not selected. In view of the organisms encountered in demonstrable bacterial infections during the 11 months of this study, and their disc sensitivities, tetracycline should have been effective in 68% of infections.

Comparability of Patient Groups: The patients included in the study and the drug administered are listed in table 1. To determine the comparability of the tetracycline- and placebo-treated patients, the two groups were analyzed as to age, sex, weight, duration of disease before and after study, infection and antibiotic therapy before and after the study, antitumor therapy during the study, hemoglobin, platelet, leukocyte, abnormal leukocyte and polymorphonuclear cell counts during the study, liver, spleen and lymph node size during the study, and the duration and degree of fever leading to inclusion in the study. No significant differences were evident for any of these factors. The response to treatment was the same, whether considered within individual groups of the randomization scheme or for the total group. For this reason the latter was used in the comparative analysis.

TABLE 2
Patients Completing the Study

	Tetracycline	Placebo
Patients started* on study	24	20
Developed infection during study	5	3
Study stopped for other reasons	0	2
Died during study	2	0
Completed two weeks of drug administration	17	15

\* Four patients were started on the study erroneously and are not included. One patient had symptoms of acute sinusitis, one had a lung infiltrate of unknown etiology, and two had an initial colony count of 1,000,000/c.c. on urine culture without urinary symptoms. The drug was stopped by the second day, and these patients are not included in any of the analyses.

† One patient developed severe folic acid antagonist toxicity and was treated for suspected

† One patient developed severe folic acid antagonist toxicity and was treated for suspected sericenia. The other patient developed urinary retention secondary to cauda equina hemorrhage, which necessitated the use of an indwelling urethral catheter. Despite an initial sterile urine culture, he died five days later with Proteus pyelonephritis and septicemia.

Table 3

Fever During the Two Weeks of Therapy in Patients Completing the Study

	Tetracycline (17)	Placebo (15)
Number of febrile days (of possible 14) (median)	7	7
Daily maximal fever (mean)	38.9	38.9
Number of episodes ending* during study	15	11
Number of recurrent† fevers after the end of an		
episode .	7	6

\* End of febrile episode defined as the last day with fever, followed by three successive afebrile days.

† Recurrence was defined as temperature in excess of 38.0° C. during the 14-day study after an episode had ended.

### RESULTS

Forty-four febrile episodes in 42 patients were studied (table 2). Thirty-two patients completed the two weeks of drug therapy, eight patients developed an infection during the study, three patients were removed from the study for other reasons (footnote, table 2), and two died before the end of the therapeutic trial.

Fever During the Study Period: No differences in the duration or severity of fever were demonstrated between patients given placebo and those given tetracycline. Comparisons of the number of days with fever during the study, the maximal, mean and minimal daily temperatures on febrile days, pulse rate, diurnal variation, duration and number of febrile episodes ending during the period of study, and recurrence of fever during the study after the end of the initial episode, failed to indicate a difference between the two groups. The results of selected analyses are presented in table 3. Figure 1 illustrates the per cent of patients in each group with fever on each of the 14 days of drug trial.

Infections During the Period of Therapy: Five of the 24 patients receiving tetracycline and three of the 20 receiving placebo developed infection

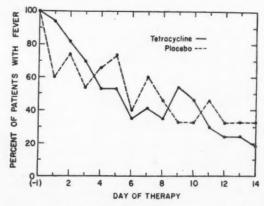


Fig. 1. Per cent of patients with fever on each day of therapy.

during the two-week period of therapy. The infections that occurred during tetracycline therapy were more severe than those which occurred during placebo administration (table 4). All four gram-negative bacillus infections occurred in patients receiving tetracycline, and the only fatal infection was in this group. Seven of the eight patients who developed infection during the study had acute leukemia.

Table 4
Infections Developing During the Two-Week Period of Therapy

	Diagnosis	Type of Infection	Organism	Outcome	Day of Study or Which Infection Began
		Tetra	acycline		
1	Acute myeloblastic leukemia	Pneumonia and septicemia	Escherichia coli	Death	11
2	Acute myeloblastic leukemia	Septicemia (cryptogenic)	Escherichia coli	Quickly cured	7
3	Multiple myeloma	Pharyngitis	Pseudomonas aeruginosa	Slowly resolved	12
4	Acute lympho- blastic leukemia	Pharyngitis	Pseudomonas aeruginosa	Slowly resolved	4
5	Acute lympho- blastic leukemia	Otitis media and bronchopneumonia	?	Quickly cured	3
-		Plac	ebo		
1*	Acute myeloblastic leukemia	Enteritis and septicemia	Clostridium septicum	Slowly resolved	9
2	Acute lympho- blastic leukemia	Bronchopneumonia	?	Quickly cured	2
3	Acute lympho- blastic leukemia	Tooth abscess	3	Quickly cured	7

<sup>\*</sup> Previously reported.27

Changes in Microbial Flora: The bacterial flora of the pharynx and the stool at the start of therapy did not differ between the group receiving tetracycline and that receiving placebo. The relative frequency of the various bacteria in initial cultures is listed in table 5. The majority of patients had "normal flora."

Pathogenic bacteria \* were the predominant organisms in pharyngeal cultures in less than 10% of cultures obtained either before or during placebo

<sup>\*</sup> Staphylococcus aureus, Pseudomonas aeruginosa, beta hemolytic streptococcus, pneumococcus, Escherichia coli, and various species of proteus, klebsiella, clostridium and salmonella.

TABLE 5
Results of Initial Culture of Pharynx and Stool

	Per Cent of Cultu Each Org	
C n	Pharynx (39)	Stool (44)
Gram-positive Bacteria		
Staphylococcus aureus, coagulase-positive	38	23
Staphylococcus albus, coagulase-negative	13	52
Staphylococcus albus, coagulase-positive	2	0
Streptococcus, beta hemolytic*	21	11
Streptococcus, gamma hemolytic	69	75
Streptococcus, alpha hemolytic	90	27
Micrococcus species	28	7
Neisseria species	69	0
Diphtheroids	33	61
Pneumococcus	5 5	0
Lactobacillus	5	50
Clostridium species	0	36
Gram-negative Bacteria		
Hemophilus species	26	0
Escherichia coli	18	98
Klebsiella species		0
Proteus species	3 5 5 3	45
Pseudomonas aeruginosa	5	7
Aerobacter aerogenes	3	30
Paracolon	0	18
Bacillus species	0	5
Fungi		
Candida albicans	5	16
Other Candida species	0	11

\* Two of the eight in the pharynx and all in the stool were enterococci. Six of the eight beta streptococci in the pharynx were in the placebo group; with this exception, no suggestive differences existed between the two groups.

administration. In contrast, pathogenic bacteria, especially coagulase-positive Staphylococcus aureus, were significantly more common (P = < 0.05) after two weeks of tetracycline therapy, and this change persisted for two weeks after the drug was discontinued (table 6).

Alterations in the fecal bacterial spectrum were less pronounced. Five of 14 stool cultures contained a staphylococcus as the predominant organism

Table 6
Pathogenic Bacteria as the Predominant Organism in Pharyngeal Culture
During Tetracycline Therapy

	Time of Culture			
	Before Therapy	After One Week of Therapy	Three Days After Therapy was Stopped	Two Weeks After Therapy was Stopped
Number of cultures Per cent of times each pathogenic organism was predominant	21	13	13	10
Staphylococcus aureus (coag. +) Escherichia coli Pseudomonas aeruginosa	0 5 0	8 0 8	38 8 8	30 10 0
Total	5	15	54	40

at the end of tetracycline therapy, compared to one of 23 before tetracycline was begun. However, four of these were coagulase-negative *Staphylococcus albus*, and no patient developed enteritis during tetracycline therapy.

Candida species were isolated from less than 10% of pharyngeal cultures and less than 33% of stool cultures in patients receiving placebo therapy. Candida was more frequently demonstrated in patients receiving tetracycline therapy (table 7). Two patients receiving tetracycline therapy developed oral moniliasis, and one developed this complication during the placebo administration.

Table 7
Frequency of Candida Isolation in Patients Receiving Tetracycline

	Time of Culture			
	Before Therapy	After One Week of Therapy	Three Days After Therapy was Stopped	Two Weeks After Therapy was Stopped
Pharynx—No. of cultures Per cent of cultures with Candida* species	21 5	13 46	13 15	10 40
Stool—No. of cultures	23	12	14	10
Per cent of cultures with Candida species	22	67	50	30

<sup>\*</sup> Of the 14 Candida species, nine were C. albicans, two were C. guilliermondi, two were C. tropicalis and one was C. pseudotropicalis.

Tetracycline Toxicity: Nausea and vomiting occurred in seven of 24 patients receiving tetracycline and in five of 20 receiving placebo. The severity of symptoms led to temporary omission of the drug in two patients in each group. However, some of the patients were also receiving antitumor agents which are capable of producing gastrointestinal symptoms.

#### DISCUSSION

The hypothesis that fever of undetermined etiology in malignant neoplastic disease may be due to occult bacterial infection rests on the demonstration of bacteria within tumor areas,² loss of fever with antibiotic therapy in uncontrolled studies,¹¹¹³ and the rationale that, since patients with acute leukemia may not respond with cellular exudates to bacterial infection,³¹¹¹⁰ infection may not be easily demonstrable. Consequently, a trial of antibiotic therapy in fever of undetermined etiology has been suggested.¹¹³ In the investigation that led to this study, the evidence against a significant portion of fever of undetermined etiology being on an infectious basis was detailed.⁴ Briefly, such fever is about evenly distributed throughout the course of neoplastic disease, while frank infection becomes increasingly frequent as the disease progresses. Autopsy fails to disclose occult infection in most patients who die during episodes of fever of undetermined etiology,

and, although the control was not ideal, a variety of antibiotics failed to influence the duration of fever. The failure of tetracycline to reduce fever in this controlled study provides conclusive evidence in this regard.

Attempts at prophylaxis of nonspecific bacterial infections have generally been unsuccessful. The frequency of bacterial infection is not decreased and its seriousness may be increased by routine antibiotic use in the post-operative period following transurethral resection, 12 gastrectomy, 12 orthopedic 13 and general surgery, 14, 15 or in measles, 16 pertussis, 17 poliomyelitis, 18, 19 urinary catheterization, 20 acute cardiac failure, 21 and in unconscious patients. 22 Good results have been reported by McVay et al. in patients with diabetes 23 and congestive heart failure. 24 Good results are also reported in the long-term therapy of chronic respiratory infections, 25 and the success of prophylaxis of a specific bacterium 26 is well established.

Our experience with a brief course of tetracycline in patients with decreased host defense against bacterial invasion was similar to many of the above studies. Infection during the period of therapy was severe, and more infections were encountered during tetracycline therapy than with the placebo. Bacterial ecology was unfavorably altered, with *Staphylococcus aureus* emerging as the predominant organism in the pharynx of many patients, and the frequency of *Candida albicans* isolation being enhanced. The incidence of superinfection is exceptionally high with antibiotic therapy of infections in patients with neoplastic disease, particularly the leukemias.<sup>1, 4, 5, 6</sup> This is probably dependent upon the inadequacy of host defense at either the local or the systemic level. Unless concurrent improvement in host defense can be achieved in addition to the successful antibiotic therapy of an infection, another organism, resistant to the antibiotic in use, emerges from the host's flora and often produces further infection.

The origin of the fever of malignancy remains obscure. None of the various theories 4 satisfactorily explains the obscure relation of fever of undetermined etiology to the malignant process. Such fever, although rare in patients in clinical remission, does not increase with increasing disease duration, and does not correlate with any particular manifestation or location of the neoplasm. Fever cannot be considered as a characteristic of any broad designation of neoplastic disease, such as the lymphomas, for although common with acute lymphoblastic leukemia and Hodgkin's disease, it is rare with chronic lymphocytic leukemia. The primary determinant of fever appears to be the specific type of neoplastic disease.

#### Conclusions

A controlled study of the effect of tetracycline on fever of undetermined etiology in malignant neoplastic disease revealed the following:

- 1. Such fever was not favorably influenced by tetracycline therapy.
- 2. Infection developed during the period of therapy in 21% of patients receiving tetracycline and in 15% of those receiving a placebo.

- The infections that developed on tetracycline were more severe, and one was fatal.
- 4. The bacterial flora of patients receiving tetracycline was altered unfavorably.
- 5. A trial of antibiotic therapy is not recommended in patients with fever without demonstrable infection.

## ACKNOWLEDGMENT

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#### SUMMARIO IN INTERLINGUA

Le etiologia de febre in patientes con morbo neoplastic in qui nulle infection es demonstrabile remane obscur. Le occurrentia occulte de un infection ha essite considerate como le possibile etiologia de tal formas de febre, e le essayo de therapia a antibioticos esseva recommendate per plure autores. Le presente studio esseva effectuate pro determinor le effecto de tetracyclina in febre de etiologia indeterminate intra le quadro de un situation controlate.

Quaranta-quatro patientes con leucemia, lymphoma, o carcinoma esseva studiate per medio de un technica bis-occulte. Omne le patientes habeva grados significative de febre, e nulle infection esseva demonstrabile clinicamente o per culturas viro- o bacteriologic. Vinti-quatro del patientes recipeva tetracyclina durante duo septi-

manas. Vinti recipeva un placebo.

Nulle differentia poteva esser recognoscite inter le duo gruppos con respecto al duration o al character del febre durante le periodo del therapia. Le patientes qui recipeva tetracyclina monstrava un disfavorabile alteration del flora bacterial del pharynge, manifeste primarimente in le emersion de Staphylococcus aureus como le organismo predominante. Le isolation de Candida albicans ab le feces esseva similemente promovite in patientes qui recipeva le tetracyclina. Octo patientes disveloppava infectiones durante le periodo del therapia. Cinque de illes pertineva al gruppo recipiente tetracyclina, e lor infectiones tendeva a esser de natura plus serie que illos in le tres patientes del gruppo a placebo.

Nostre conclusion es que febre occurrente in le absentia de demonstrabile infectiones es usualmente non causate per infectiones occulte. In tal casos, therapia a antibioticos non pote esser recommendate, proque nulle beneficio "prophylactic" esseva demonstrate, e le infectiones que interveniva esseva plus serie in consequentia

del alterate ecologia bacterial.

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# SIGNIFICANCE OF SMALL PLEURAL EFFUSIONS IN CARDIOPULMONARY DISEASE, AND SOME OTHER OBSERVATIONS ON PLEURAL FLUID IN GENERAL \* †

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THAT massive pleural effusion or hydrothorax may precipitate severe dyspnea and air hunger and be an immediate threat to life, requiring emergency thoracentesis, is universally recognized. On the other hand, even a massive pleural effusion of the common idiopathic type, which is associated with relatively little disease of the underlying lung, is frequently well tolerated, particularly if it be unilateral, and in a young adult with a normal heart and a normal contralateral lung. Under these circumstances, as much as 2,000 to 3,000 ml. of fluid may produce relatively little discomfort-perhaps only a little dyspnea or breathlessness on mild exertion. However, it is not widely recognized that, in the presence of antecedent cardiac or pulmonary disease which already seriously interferes with pulmonary function and causes difficulty in breathing, the accumulation of even a small amount of fluid in one or both pleural cavities may precipitate a critical degree of anoxia, dyspnea and air hunger, and even cause death. This occurs most commonly in middle aged or elderly individuals with coexistent congestive heart failure and pulmonary emphysema or fibrosis; but a similar situation may arise when congestive heart failure is complicated by one or more areas of pneumonia, pulmonary infarction, atelectasis or other pathologic processes which, together, compromise pulmonary function to the point where the final added increment of a small pleural effusion tips the scale in the direction of complete respiratory decompensation. As a corollary, recognition and removal of such a relatively small amount of free pleural fluid by timely thoracentesis are frequently lifesaving.

The significance of small amounts of pleural fluid in precipitating acute air hunger and death by asphyxia is frequently not realized because (1) there appear to be sufficient reasons in the presence of congestive heart failure, cardiac asthma and pulmonary edema to explain the severe dyspnea and orthopnea; (2) in the presence of the associated underlying pathologic conditions, such small amounts of pleural fluid may be difficult to detect by means of physical and x-ray examination, and (3) unfortunately too often,

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<sup>†</sup> Since in this paper we are concerned only with the mechanical effects of pleural fluid, the terms "hydrothorax" and "pleural effusion" will be used interchangeably.

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estimation of the degree of deleterious effect of a given amount of free pleural fluid is based in the mind of the physician on the scale of the young individual with normal heart and contralateral lung who can tolerate a large amount of fluid (just as he can a complete unilateral pneumonectomy) with relatively little discomfort. The thought then occurs that the amount of fluid is not sufficient to cause dyspnea or to warrant tapping, and all of the patient's discomfort, restlessness and dyspnea are erroneously attributed to the underlying disease, even until his death.

How often, at the autopsy of a patient who has died in heart failure, do we hear the pathologist state, "There are 600 ml. of fluid in the right pleural cavity and 400 ml. in the left" (or somewhat smaller or larger amounts), without recognition by the pathologist or the clinician of the possible significance of this amount of pleural fluid as the immediate cause of the patient's death. The presence of such "small amounts" of fluid may not even be considered to be important enough to be included in the final anatomic diagnosis or mentioned in the death certificate.

In figure 1 we have attempted to illustrate diagrammatically the "summation concept" in the causation of air hunger by pleural fluid. Let us say that the symptoms of extreme dyspnea which we call air hunger will appear in a given individual when one or more of a number of factors—pulmonary congestion and edema (secondary to heart failure, myocardial infarction or valvular disease); pulmonary emphysema or fibrosis; pneumonia, infarction or atelectasis; diffuse bronchial disease or obstruction; and pleural fluid—have encroached upon and compromised reserve pulmonary function to a critical figure x. It is apparent that the closer to this degree of functional pulmonary impairment one or more of these factors have led the patient, the smaller will be the final increment of free pleural fluid necessary to reach this critical level and to precipitate air hunger.

This concept has been well expressed by Altschule 1 as follows: "the changes in pulmonary function caused by hydrothorax are however similar in some ways to those consequent to emphysema, diffuse pulmonary fibrosis or congestive heart failure. Accordingly, patients with diffuse pulmonary disease, emphysema, fibrosis or congestion are more likely to exhibit dyspnea and orthopnea when pleural fluid develops than are other patients. The severity of respiratory symptoms varies not only with the volume of fluid in the pleural spaces, but with the severity of the underlying disease. Conversely, if a patient obtains marked relief from respiratory discomfort following a relatively small thoracentesis, it is likely that he also had some diffuse pulmonary lesion."

In our experience, as little as 500 ml. of fluid (whether entirely in one pleural cavity or divided between the two) may be critical—"the straw that breaks the camel's back"—and removal of even such a small amount of fluid under these circumstances may be a lifesaving measure. This is not to say that such small amounts of fluid, if marked dyspnea or air hunger is not present, are necessarily indications for thoracentesis; but when these

symptoms are present, then thoracentesis is obligatory without delay, even as an emergency at night.

The recognition of such small amounts of pleural fluid by the methods of physical diagnosis may be extremely difficult in the presence of pathologic pulmonary alterations produced by acute or chronic heart or lung disease; and the differential diagnosis—which under these conditions must be based primarily on impairment of resonance over the region of fluid—from such

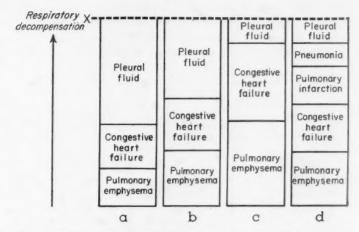


Fig. 1. Diagrammatic representation of the "summation concept" in dyspnea due to a combination of pulmonary emphysema, congestive heart failure and pleural fluid. Long vertical rectangles represent reserve pulmonary function. a. Reserve pulmonary function partially compromised by minimal degrees of pulmonary emphysema and congestive heart failure, present together. Large amount of superimposed pleural fluid necessary to compromise remaining reserve pulmonary function to the point of respiratory decompensation and air hunger. b. Reserve pulmonary function compromised to a greater extent by moderate degrees of pulmonary emphysema and congestive heart failure, present together. Lesser amount of super-added pleural fluid (than in a) now suffices to compromise reserve pulmonary function compromised to still greater extent by severe degrees of pulmonary emphysema and congestive heart failure, present together. Small amount of super-added pleural fluid now suffices to compromise remaining reserve pulmonary function to the point of respiratory decompensation. d. Reserve pulmonary function partially compromised by moderate degrees of pulmonary emphysema and congestive heart failure, present together; but complicating pulmonary emphysema and congestive heart failure, present together; but complicating pulmonary infarction and pneumonia compromise another large increment of reserve pulmonary function. Here, too, small amount of super-added pleural fluid now suffices to compromise remaining reserve pulmonary function to the point of respiratory decompensation.

conditions as pulmonary atelectasis, infarction, pneumonia, edema, thickened pleura and elevated diaphragm may be virtually impossible. The classic signs of massive effusion or hydrothorax—flatness on percussion, absent fremitus and breath sounds, shift of the heart and mediastinum to the opposite side, skodaic resonance and bronchovesicular breath sounds above the fluid, and Grocco's triangle on the other side—are not obtained with the small amounts of fluid being dealt with here.

The amount of fluid corresponding to a given vertical height of percussion dullness in the patient with an emphysematous chest is frequently seriously underestimated, for several reasons:

1. Impairment of resonance due to fluid may be masked or its extent diminished by the hyperresonance of the associated emphysema.

2. The same volume of fluid will rise to a much higher vertical level, and thus be more easily detectable on percussion, in the normal flat, narrow chest than in the broad, barrel chest of the patient with chronic pulmonary emphysema, in which the fluid will spread out and lie in a much thinner

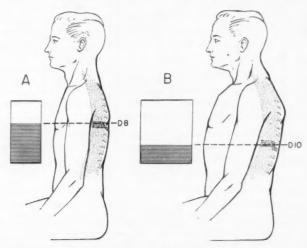


Fig. 2. Factors affecting the upper levels of fluid in the normal and emphysematous chests. A and B. A given amount of pleural fluid (e.g., 1,000 ml.) rises to a higher level in the normal flat, narrow chest (A) than in the barrel chest of a large diameter of chronic hypertrophic pulmonary emphysema (B), in which it spreads out in a thinner layer over the broad basal diaphragmatic area of the pleural cavity. The upper level of the fluid may reach to the level of D 8 in the former, but only to the level of D 10 in the latter. Similarly, the same amount of fluid rises higher in the narrow cylinder (A) than in the broad cylinder (B).

layer over the larger basal (diaphragmatic) area of the pleural cavity (figures 2A and B), although the volume of lung compressed and rendered functionless in each case may be the same. Specifically, 1,000 ml. of fluid may elicit an upper level of dullness posteriorly at the level of the eighth or seventh dorsal vertebra (D 8 or D 7) in the former, but only to the level of D 10 or D 9 in the latter, an extent of dullness which may not be considered to be significant by the examiner.

3. Because of the flattening and depression of the diaphragm in the emphysematous chest, the base on which the fluid rests is lower than in the normal chest, and the upper extent of dullness is therefore also lower.

4. A point of great importance is the fact that the overdistended, inelastic, emphysematous lung extends to the lower limits of the pleural cavity throughout the respiratory cycle, so that the lower level of pulmonary resonance during expiration, which lies at the level of D 10 posteriorly in the normal chest, extends down to the level of D 12 in the emphysematous patient. Therefore, dullness even in this region (between D 12 and D 10) may be abnormal in the emphysematous patient, and indicative of fluid (figure 3).

5. Finally, bronchial breath sounds, rather than diminished or absent breath sounds, may be heard over a small collection of fluid, as it is occasionally over a large effusion (Baccelli's phenomenon), and be misinterpreted as consolidation of the lung of variable etiology, rather than as pleural fluid.

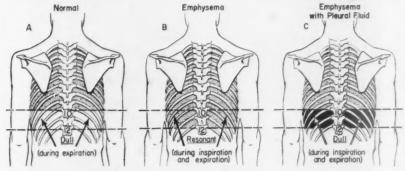


Fig. 3. Significance of dullness on percussion between the levels of D 12 and D 10 in the normal and the emphysematous chest. A. In the normal chest the lower limits of the lungs, and resonance on percussion, extend to the level of D 10 during expiration and to D 12 only during deep inspiration. B. In the emphysematous chest the inelastic and over-distended lungs, and resonance on percussion, extend to the lower limits of the pleural cavity during both inspiration and expiration. C. Emphysematous chest with pleural fluid (black) between D 12 and D 10. Dullness on percussion between D 12 and D 10, which is expected in the normal chest, is abnormal in the emphysematous chest, and is suggestive of possible pleural fluid.

Under these conditions, a high index of suspicion that any degree and extent of impairment of resonance, particularly over the dependent portions of the chest posteriorly, may represent a significant collection of free pleural fluid, and the testing of this suspicion in patients with dyspnea by the free and uninhibited use of exploratory thoracentesis, are the only assurance that some of these patients will be relieved of their dyspnea or saved from immediate death by asphyxia. Occasional dry taps will occur but, if properly performed, will do no harm.

Technic. Because of the small amounts of fluid involved, and the occasional necessity for doing several exploratory punctures on one or both sides at the same sitting, the technic of the procedure must be meticulous, aseptic, painless and precise. To these ends, the most important features of our technic are (1) the use of 2% (rather than 1%) Novocaine, for more potent and quicker anesthesia; (2) the

preliminary raising of an intradermal wheal with this solution and a fine hypodermic (25-gauge) needle; once this is produced, the procedure becomes entirely painless; without it, the injection of even large amounts of anesthetic solution subcutaneously and into the deeper tissues rarely produces adequate anesthesia; (3) the subsequent use of a long (2 to  $2\frac{1}{2}$  inches) thin (22-gauge) exploring needle to discover and verify the presence of fluid; (4) substitution of a larger bore (17- or 18-gauge) thoracentesis needle for the actual drainage of the fluid, to hasten the procedure and to lessen the chance of obstruction of the needle by a small plug of fibrin; (5) continual injection of the local anesthetic solution ahead of the needle tip as the latter is advanced, so that the needle constantly proceeds in a previously anesthetized tract;

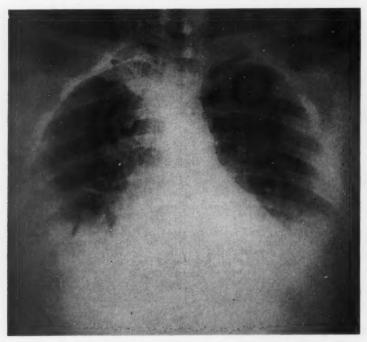


Fig. 4. Case 1. Bedside chest x-ray, 4/21/55, one hour before bilateral thoracentesis yielded 350 ml. from the left hemithorax and 250 ml. from the right (total amounts obtainable). X-ray report: "Changes of pulmonary passive congestion . . . pleural fluid in the right and left hemithoraces, and in the horizontal fissure of the right lung."

and (6) use of a Wangensteen suction apparatus to drain the pleural fluid, involving no effort on the part of the operator, leaving both of his hands free, and providing a steady free flow of fluid (under the constant observation of the operator) from the pleural cavity into the collecting bottle. Rarely are more than 2 to 3 ml. of local anesthetic solution required for adequate anesthesia for any single puncture.

The site of thoracentesis is established near the lower margin of the suspected fluid as determined by percussion dullness or x-ray, in the position the patient is to be in during the procedure. Because of extreme illness or weakness of the patient, this is often the lateral decubitus, with the subject lying on the side opposite to that

which is to be punctured. Orthopnea, which is frequently present, may require lateral decubitus in the semi-sitting position on a back rest. The procedure is simplified if the patient is strong enough to sit up in bed with his back to the operator, his feet dangling over the edge of the bed or resting on a chair at the bedside.

When less than 1,000 ml. of fluid are estimated to be present, the site of puncture is most often in the eleventh, tenth or ninth interspace, midway between the bordering ribs or at the upper margin of the lower one, in a vertical line midway between the lateral border of the spine and the posterior axillary line; or in the midscapular line. The needle is not introduced too close to the borders of the spine (within 2 inches)



Fig. 5. Case 10. Posteroanterior view of chest, 12/7/56. X-ray report: "Enlarged heart . . . some enlargement to the right and suspicion of cor pulmonale . . . lung markings suggestive of chronic bronchitis and emphysema." No mention of pleural fluid in x-ray report. No evidence of fluid on this film.

for fear of entering the great vessels or a chamber of the heart. Because the needle is introduced so low in the chest cage, the tip comes to lie in the very narrow costophrenic space, and may repeatedly have to be positioned slightly to keep it within the lumen of the pleural cavity and to maintain a free flow of fluid.

We remove all of the fluid obtainable, to achieve the maximal benefit and relief of dyspnea and to prolong the period between tappings, if these should prove necessary. The danger of precipitation of acute pulmonary edema by complete removal of the fluid, with resulting rapid reexpansion of the lung, is remote, especially with the relatively small amounts of fluid being considered here. We have never seen a case of "pleural shock," although we use no premedication routinely.

Perhaps the continual injection of the anesthetic solution *ahead* of the needle tip, so that the pleura is anesthetized before the needle punctures it, is a factor in this favorable experience.

Of all of the factors which, together, are causing severe dyspnea and immediately threatening life, that of compression of the lung by pleural fluid is the only one (except perhaps obstruction of the airway by edema fluid

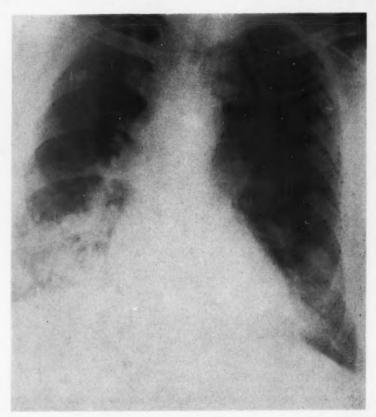


Fig. 6. Case 11. Bedside chest x-ray, 9/6/55. X-ray report: "Generalized density over both bases through which we see accentuated vessel markings . . . we are dealing mainly with pulmonary congestion." Pleural fluid not mentioned.

or retained bronchial secretions which can be removed by catheter aspiration) which lends itself to immediate correction by mechanical removal, and recognition is therefore of great importance. The timely reprieve afforded by mechanical removal of the fluid may then tide the patient over, and permit spontaneous or therapeutically induced cure of the underlying disease. A most pernicious thing in these trying circumstances is to fear

or to neglect to turn the patient on his side, or to sit him up, to examine the posterior aspects of the chest "because he is too sick." No dyspneic patient is too sick to have his back examined, and he may die if this is not done. Patients with acute or chronic heart or lung disease usually tolerate the orthopneic or sitting position better than any other.



Fig. 7. Case 12. Chest x-ray, 1/24/56. X-ray report: "Cardiac enlargement and pulmonary congestion." Pleural fluid not mentioned.

Nor can x-ray of the chest be relied upon as it is too frequently, to be the final arbiter to exclude significant amounts of free pleural fluid under the conditions being considered. There are several reasons for this:

1. The urgency of the patient's condition is often too great to wait for or to permit the taking, developing and examination of the films; the patient may be too dyspneic and restless to cooperate; or administration of oxygen cannot be discontinued for the time required to take the films.

2. The films taken with the portable machine at the bedside may be unsatisfactory.

3. More important than these factors, however, is the fact that the amounts of fluid we are considering here may not appear or be recognizable

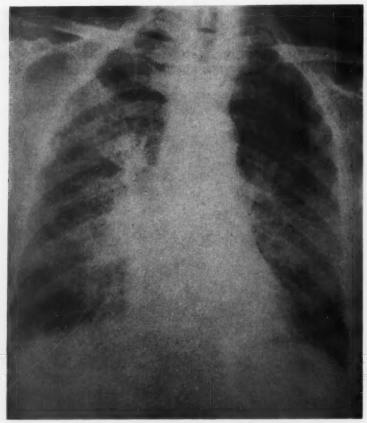


Fig. 8A. Case 13. Posteroanterior chest x-ray, 10/7/53. X-ray report: "Both hemi-diaphragms are flattened . . . the right costo-phrenic angle is slightly obscured due to a very small pleural effusion . . . numerous mottled densities in both lung fields, which could be due to tuberculosis, fungus infection or widespread carcinomatosis . . . heart slightly enlarged in its transverse diameter, with some flattening of the left border indicative of myocardial damage." Thoracentesis of the right hemithorax immediately following this x-ray examination yielded 800 ml. of pleural fluid.

in the films (figures 5, 6, 7, 8, 9). The capacity of the costophrenic gutter is very variable, depending upon its size and shape, and has been estimated to be between 400 and 600 ml.; however, in the barrel chest of large circumference and basal area of emphysema, it may easily accommodate up to 1,000 ml. of fluid. The x-ray diagnosis of "obliteration," "blunting" or "haziness" of the costophrenic angle is then too frequently interpreted as indicating too small an amount of fluid to account for symptoms or to warrant tapping.

4. With deep costophrenic angles there may be a considerable amount of fluid which follows the outline of the diaphragm and maintains the acute-

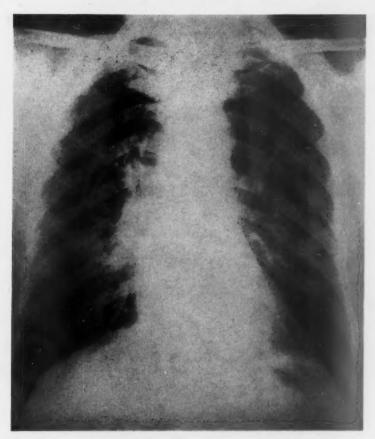


Fig. 8B. Case 13. Repeat posteroanterior chest x-ray, 10/16/53. X-ray report: "The infiltrations throughout both lung fields have cleared up considerably...some fullness in both hilar regions... remainder of the lungs is relatively well aerated... the cardiac silhouette is normal."

ness of the costophrenic angle so that fluid is not suspected; the true depth and shape of the costophrenic gutter and the actual amount of fluid present become apparent only after the fluid is removed mechanically or recedes spontaneously (figures 8A, B, C, and 9).

- 5. Infrapulmonary, supradiaphragmatic basal collections of fluid may occur and be demonstrable only by special maneuvers and positions (such as the lateral decubitus) under the x-ray.
- 6. If the film must be taken with the patient in the lying position, the fluid may spread out over the entire posterior aspect of the lung and give a generalized haziness, without an upper level or curve which can be recognized as fluid.



Fig. 8C. Case 13. Repeat posteroanterior chest x-ray, 10/19/53. Note the successive deepening of the costophrenic angles, especially the right, in the successive posteroanterior views. The true depth of the costophrenic angle is evident only when all of the pleural fluid has disappeared.

7. The lack of contrast between the heavy, congested and edematous or "drowned" lung and pleural fluid, as compared to the usually sharp contrast between normal air-containing lung and free pleural fluid, may make the x-ray recognition of the fluid difficult or impossible (figures 6 and 7).

8. Fluid in the left chest may be completely hidden behind the heart shadow, particularly if the heart be markedly enlarged.

9. The fluid may be entirely hidden in the posteroanterior view by the bulge of the diaphragm, and its presence be recognizable only in a lateral view, if the latter can be taken (figures 5 and 8).

10. Encapsulation of fluid by adhesions which extend along the course

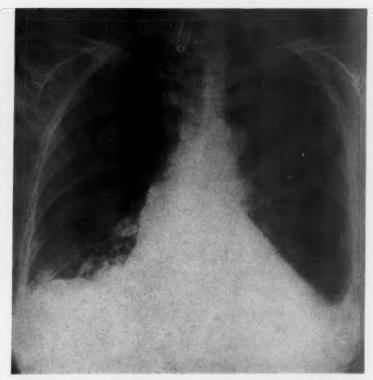


Fig. 9A. Case 14. Chest x-ray, 12/2/56. X-ray report: "Enlarged heart with hypertensive configuration . . . sclerotic aortic knob . . . lungs show increased markings of bilateral congestion and calcified nodes in the right sub-clavicular area." Pleural fluid not mentioned.

of a main or secondary interlobar fissure may simulate consolidation of a lobe by pneumonia, infarction or atelectasis, rather than pleural fluid.

11. Interlobar collections of fluid may give atypical shadows, or require special positioning for demonstration.

12. Soft-tissue shadows and large breasts may obscure the costophrenic angles and lead to the overlooking of a significant amount of pleural fluid (case 16).

13. The terms "pleuritic reaction" and "pleural thickening," often used in x-ray reports, are misleading, beg the question, and often obscure the diagnosis of free pleural fluid (case 17). On many occasions in our experience when the chest x-ray—taken with the standard technic in the x-ray department, or with a portable machine at the bedside—was not interpreted as demonstrating free pleural fluid, but impairment of resonance suggestive of fluid was present, thoracentesis has yielded from 500 to 2,000 ml. of

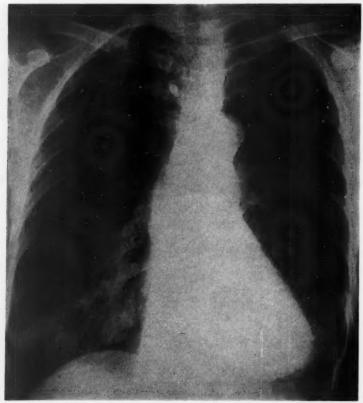


Fig. 9B. Case 14. Repeat chest x-ray 12/27/56. X-ray report: "The lungs are negative... the heart appears within normal limits... the aorta is elongated and tortuous with calcification in the knob." Note the deepening of the costophrenic angles in the successive x-rays. The true depth of the costophrenic sinuses is apparent only after the pleural fluid has disappeared.

fluid, with immediate, dramatic and frequently lifesaving amelioration of dyspnea, air hunger and restlessness (cases 10, 11, 12, 13, 14; figures 5, 6, 7, 8, 9). Admittedly, the reverse also occurs, and the x-ray may disclose smaller or larger amounts of fluid not suspected or demonstrable on physical examination.

Many of the considerations discussed above have been known to previous and to contemporary observers. Altschule's comments have already been mentioned. Concerning the diagnosis of small pleural effusions, Cabot <sup>2</sup> wrote: "An effusion amounting to a pint should always be recognizable, and smaller amounts have frequently been diagnosed and proved by puncture. . . . It is very common to find on puncture an amount of fluid much greater than could have been suspected from the percussion out-

lines. . . . When hyperresonance of the sound side is suspected it should warn us to percuss lightly over the effusion, else we may bring out the resonance of the distended lung. . . . If the lung on the affected side fails to retract (owing to emphysema or adhesions to the chest wall) the area of dullness and its intensity will be much diminished. . . . Tubular sounds only may be produced because only the bronchi remain open, the rest of the lung being collapsed . . . or again, if râles or friction sounds are produced in the lung they too may be transmitted to the fluid and may (alas!) deter the timid observer from tapping. . . . It is almost impossible to distinguish small fluid accumulations in the pleural cavity from pleural thickening or pulmonary atelectasis; in doubtful cases the diagnosis can and should be cleared up by puncture."

Concerning the therapeutic management of pleural effusion in cases of heart failure, White 3 states: ". . . When rest, digitalis, diuretics, and other measures fail to relieve ascites and hydrothorax, and oppression from the fluid is disagreeable, paracentesis should be done and as much fluid as possible removed from the peritoneal and pleural cavities, without exhausting the patient. This is especially important in the case of hydrothorax because of the greater embarrassment of the already difficult breathing by the reduction of the vital capacity by the pleural fluid, and because the fluid is absorbed more slowly from the pleural than from the peritoneal cavity." Friedberg,4 on the same subject, says: "When other therapeutic measures fail to relieve dyspnea, the removal of fluid from the chest is indicated even when the size of the effusion does not appear to be very large." Chapman 5 writes: "The discovery of pleural fluid demands thoracentesis. . . . Attempt at aspiration is indicated whenever pleural fluid is suspected." Barnwell,6 in discussing the same subject, says: "Since the effusion itself collapses the lung, partially splints the chest wall and diaphragm, and may place pressure upon and displace the mediastinal structures, the symptoms of dyspnea may demand its immediate removal. . . . Depending upon the size of the effusion, in some instances removal of 500 to 1000 ml. may serve only to restore mediastinal displacement, while in others it may result in a considerable re-expansion of a compressed and diseased lung." son,7 in discussing infrapulmonary supradiaphragmatic basal collections of pleural fluid, notes that "the respiratory incapacity may be quite severe, even though volumetric accumulation of fluid is relatively small," and reports, apparently with considerable surprise, that in one of his cases 700 ml. of fluid caused great respiratory distress, and that "respiratory function was completely restored to normal by aspiration of this relatively small amount of fluid"!

## CASE REPORTS

# I. Small Pleural Effusions

Case 1. A 48 year old obese, emphysematous man was seen with his family physician on April 20, 1955, because of acute anterior myocardial infarction, with

typical electrocardiographic findings, for which he had been hospitalized several days previously. The patient was acutely ill, with flushed face, fever, regular tachypnea, respiratory mobility of the alae nasi, distant heart tones, gallop rhythm, bronchial breathing and bronchophony over the pulmonary bases posteriorly, and crepitant râles in the right lower lobe. The findings in the lungs were interpreted as indicative of one or more pulmonary complications of the cardiac lesion, namely, pneumonia, infarction, atelectasis or edema. A small amount of pleural fluid could not be excluded. Digitalis and antibiotics were being administered.

Dyspnea and cyanosis became extreme at 6:00 a.m. the next day, requiring the continuous administration of 100% oxygen by means of a BLB mask. When seen three hours later, the patient was markedly dyspneic, cyanotic, restless, apprehensive and perspiring. The respiratory rate was 48, the blood pressure, 116/80 mm. of Hg. Slight but definite impairment of resonance was noted "very low down" over both sides of the chest posteriorly, more pronounced on the left. Although the diagnosis of free pleural fluid could not be made with certainty from these findings, an emergency bedside chest x-ray (figure 4) which had been taken earlier that morning seemed to confirm the presence of free pleural fluid. Bilateral thoracentesis (with the patient lying first on the right side and then on the left) yielded 350 ml. of amber fluid from the left side and 250 ml. from the right (for a total of 600 ml.). There was immediate and striking subjective and objective improvement in the patient's breathing; respirations were slower and deeper, and the oxygen mask was no longer needed. The patient was relaxed and thankful, and fell into a quiet sleep in the oxygen tent. Mercuhydrin was added to the therapeutic régime. Subsequent recovery was uneventful.

Case 2. A 60 year old obese, emphysematous, diabetic woman suffered an acute coronary occlusion on February 21, 1949, with typical symptomatology and electrocardiographic findings, and was hospitalized on this date. She did well and was asymptomatic after the first day of illness until one week later when, in the evening of March 1, she developed extreme restlessness (tossing about in bed from side to side), a sensation of pressure and weight in the chest, back and upper abdomen, and progressive dyspnea. She was extremely apprehensive and uncomfortable. Examination disclosed flatness to percussion and diminished to absent breath sounds over the right side of the chest posteriorly below D 9. The patient's condition was so acute that it was deemed inadvisable to wait for a chest x-ray. Emergency thoracentesis vielded 800 ml. of straw-colored fluid from the right pleural cavity, with immediate and complete relief of the dyspnea and discomfort; the patient soon fell

into a quiet and relaxed sleep. Subsequently, recovery was uneventful.

Case 3. A 52 year old man was seen on June 28, 1952, in chronic congestive failure, in spite of treatment with digitalis, quinidine, Mercuhydrin and Demerol, since he had suffered an acute coronary occlusion several years previously. During

this period he had several episodes of pulmonary infarction.

Presenting complaints on this hospital admission were acute, pleuritic type of right chest pain, dyspnea, cyanosis, slight hacking cough, and tachycardia with frequent extrasystoles for several days. There had been no hemoptysis. Physical examination disclosed a large, globular heart, marked dullness over the lower half of the right lower lobe with generally diminished breath sounds, and one focus of distant bronchial breathing and crepitant râles in this area. Numerous moist râles were present in the left lower lobe posteriorly. Grocco's sign on the left was negative. The liver was palpably enlarged. Ascites and edema were absent. The electrocardiogram revealed low voltage in all leads. The diagnosis was chronic arteriosclerotic heart disease with failure, and acute pulmonary infarction of the right lower lobe.

On July 6, 1952, the patient was markedly dyspneic and coughing incessantly.

Flatness on percussion was detected below D 9 posteriorly on the right, and thoracentesis in the tenth interspace yielded 600 ml. of serosanguineous fluid. Marked improvement in breathing and disappearance of the cough occurred immediately. Mercuhydrin, 2 ml. intramuscularly, was administered, and in the following 24 hours the patient voided 3,000 ml. of urine. On July 10, 1952, he had again been dyspneic for 24 hours, and 500 ml. of fluid were again removed from the right pleural cavity by thoracentesis, with immediate relief of the dyspnea. Daily improvement and

gradual recovery followed, without further thoracentesis.

Case 4. A 78 year old woman with emphysema and congestive heart failure due to long-standing hypertensive and arteriosclerotic heart disease was seen in a state of acute air hunger, with marked restlessness and dyspnea, which had developed in spite of and during the course of routine medical management for heart failure. Rapid and cursory examination, because of the patient's restlessness and continual motion, disclosed moderate impairment of resonance over both pulmonary bases posteriorly. Immediate sequential bilateral thoracentesis yielded 600 ml. from the right chest and 400 ml. from the left (a combined total of 1,000 ml.) of clear, straw-colored fluid. Relief of air hunger was immediate and remarkable. Restlessness disappeared, and breathing was much easier, slower and deeper. Ultimate recovery occurred on continued treatment with bed-rest, digitalis and Mercuhydrin.

Case 5. A 52 year old emphysematous woman with a history of rheumatic heart disease, previous episodes of decompensation and, in the last three months, chronic congestive heart failure, was seen on May 20, 1954, because of marked dyspnea and restlessness. The patient was also nauseated and vomiting from digitalis intoxication. The apical heart rate was 72, with the absolute irregularity of auricular fibrillation. A loud systolic murmur was audible all over the precordium. Generalized subcutaneous edema and ascites were present. Impaired resonance was elicited below the level of D 9 on the right side and D 10 on the left. Immediate thoracentesis yielded 700 ml. from the right pleural cavity and 400 ml. from the left (needle in the tenth interspace on the right, the eleventh on the left), a total of 1,100 ml., with marked and prompt relief of the dyspnea and restlessness. The immediate disappearance of the acute emergency was spectacular. Digitalis

was discontinued temporarily.

Case 6. A 60 year old man with an emphysematous chest, hypertensive and arteriosclerotic heart disease, and chronic congestive heart failure, was seen with his family physician on June 26, 1953. Examination disclosed a fever of 101° F. rectally, bronchial breathing, and bronchophony over the entire left lower pulmonary lobe posteriorly, a white blood cell count of 33,550, and scanty yellow sputum indicative of pneumonia or an infected pulmonary infarct. The patient apparently did well on treatment with penicillin and streptomycin until July 3, 1953, when, while straining at stool, he suddenly developed acute pulmonary edema with moist respirations, bubbling râles audible diffusely in both lungs, increase in pulse rate to 140, and blood pressure to 240/140 mm. of Hg. The possibility that the attack of acute pulmonary edema was precipitated by a pulmonary embolus could not be ex-The attack of acute pulmonary edema subsided on treatment with Demerol, oxygen by mask, venesection, and Mercuhydrin intramuscularly; but bronchial breathing and crepitant rales persisted over the left lower lobe. Dullness and diminished breath sounds were also present over the lower third of the right lobe posteriorly, with bronchial breath sounds and crepitant râles over the upper half of this lobe. On July 5, 1953, the patient was breathless and weak, the pulse was 120, the blood pressure, 170/100 mm. of Hg. Thoracentesis of the right chest yielded 500 ml. of straw-colored fluid. The patient improved at once, and breathing was much easier; the pulse rate dropped to 100. Mercuhydrin, 2 ml., was given intramuscularly. The next morning the patient suddenly became extremely dyspneic

and weak. Dullness progressing to flatness inferiorly over the lower half of the left lower lobe, and bronchial breathing up to the main interlobar fissure, were elicited on physical examination. Thoracentesis of the left chest yielded 900 ml. of slightly turbid, reddish amber colored fluid, with immediate and marked improvement in the dyspnea. Bronchial breathing persisted bilaterally after the tapping, due to the underlying pneumonic processes. From this day on the patient gradually recovered, without further thoracentesis; the abnormal physical findings subsided, and he subsequently left the hospital in good condition.

# II. Sizable Pleural Effusions Obscured by Emphysema, and Volumetrically Underestimated or Overlooked

Case 7. A 77 year old woman was admitted to the hospital on December 10, 1950, with marked dyspnea, orthopnea, cyanosis, bigeminal pulse (digitalis intoxication), and peripheral dependent edema. Mercuhydrin, 2 ml. intramuscularly, had been administered the previous day. The patient was extremely dyspneic, uncomfortable, restless and perspiring. Examination disclosed a hugely emphysematous chest, with impaired resonance bilaterally on percussion below the level of D 9 posteriorly.

Immediate thoracentesis of the right hemithorax in the tenth interspace posteriorly yielded 1,000 ml. (total amount obtainable) of a clear, greenish yellow fluid which jelled on standing, with complete relief of the dyspnea, excitement and discomfort. Fluid did not re-accumulate, and subsequent recovery was uneventful. Thoracentesis of the left chest was not necessary.

Case 8. A 78 year old woman was admitted to the hospital on May 20, 1951, with marked dyspnea and orthopnea not relieved by digitalis to the point of toxicity (nausea and vomiting); she had been given an intravenous injection of aminophylline that morning. She had been suffering with precordial pain, relieved by nitroglycerin, which had become worse in the last week.

On examination the jugular veins were engorged; the chest was hugely emphysematous in contour; the heart was enlarged to the left, of aortic configuration, with a rapid, regular rate. An apical systolic murmur, a loud aortic systolic murmur, and a thrill transmitted to the neck vessels, and marked diminution of the aortic second tone, were present and considered to be diagnostic of aortic valvular stenosis. Impairment of resonance on percussion was demonstrated below the level of D 9 on the right side posteriorly. Immediate thoracentesis in the right tenth interspace posteriorly yielded 1,000 ml. of straw-colored fluid, with immediate and spectacular relief of the dyspnea.

Case 9. A 60 year old man was seen with his attending physician on the evening of November 14, 1950. Progressively increasing dyspnea had developed in the last four days, and on the day of examination had become very severe.

Examination revealed the patient to be violently restless and wild-eyed with air hunger, moaning and tossing about in bed, and unable to talk because of dyspnea. The chest was voluminous and barrel-shaped. Moderate impairment of resonance, and absence of breath sounds between the levels of D 9 and D 12, were elicited over both pulmonary bases posteriorly. Rhonchi, expiratory wheezing and moist râles were audible elsewhere throughout both lungs. The liver extended three finger-breadths below the right costal arch, and the lower extremities were edematous. Diagnosis of congestive heart failure, pulmonary edema and bilateral hydrothorax was made.

Emergency thoracentesis was performed, first on the right side and then on the left, with removal of 1,000 ml. of straw-colored fluid from each side, all of the fluid obtainable being withdrawn. There was immediate and complete relief of the

dyspnea, and the patient became quiet, comfortable and relaxed. The signs of cardiac asthma and pulmonary edema disappeared at once. Subsequently, recovery occurred on medical therapy for cardiac failure. No further thoracentesis was required.

Comment: In these cases the degree of impairment of resonance on percussion due to the fluid in the pleural cavities was diminished by the associated pulmonary emphysema, and the areas of dullness did not extend above the level of D 9 or D 10 posteriorly, which, on casual consideration, was a very small proportion of the huge posterior surface area of the barrel chest in each case. Dullness in the area between the levels of D 9 and D 12 posteriorly had been considered to be normal and had been disregarded. It was not expected that this extent of dullness indicated the presence of as much as 1,000 ml. of fluid on one or both sides, or that enough fluid was present to contribute in any significant degree to the severe dyspnea which was present. The entire clinical picture was attributed solely to the heart failure as such, and the presence and significance of the "apparently small" hydrothoraces were overlooked. In case 9, at least, bilateral thoracentesis was a life-saving measure by a matter of minutes. In two of these patients (cases 7 and 8), digitalis had been pushed to the point of toxicity to control the "intractable heart failure."

# III. X-ray Misinterpretation of Pleural Fluid

A. "Negative Chest X-rays"

Case 10. A man 65 years of age, with an emphysematous chest contour, was seen in the hospital with his physician on December 7, 1956. Two weeks previously he had been discharged from the hospital after a stay of six weeks for treatment of an acute myocardial infarction. Since he had been at home he had suffered from almost constant breathlessness, with frequent exacerbations of acute paroxysmal dyspnea and pulmonary edema, which finally necessitated rehospitalization. Examination disclosed flatness on percussion and absent breath sounds in the right chest posteriorly below the level of D 10, suggestive of hydrothorax. Moist rales elsewhere in both lower lobes were indicative of pulmonary edema. In spite of the fact that a chest x-ray taken the same morning showed clear costophrenic angles and was interpreted as negative for pleural fluid (figure 5), exploratory thoracentesis was performed in the right tenth interspace posteriorly because of the symptoms and physical findings; this yielded 1,000 ml. of straw-colored fluid, with immediate and complete relief of all symptoms. This relief, on further observations, proved to be permanent.

Case 11. A 72 year old man with an emphysematous chest contour was seen in the hospital with his physician on September 9, 1955, in the third week of an acute posterior myocardial infarction. The patient was markedly dyspneic, even while lying in an oxygen tent. Examination revealed dullness progressing to flatness in the right chest posteriorly below the level of D 9, with absent fremitus and breath sounds, indicative of free pleural fluid. X-ray of the chest on September 6 (figure 6) was interpreted as showing accentuated basilar vessel markings, indicative of pulmonary congestion, but no pleural fluid. Exploratory thoracentesis in the right tenth interspace posteriorly, performed because of the symptoms and physical findings,

yielded 1,100 ml. of thin, straw-colored fluid, with immediate and considerable relief of the dyspnea. Treatment for congestive heart failure was instituted, with ultimate

recovery of the patient.

Case 12. An 81 year old woman with pulmonary emphysema and arteriosclerotic heart disease had been treated in the hospital for congestive heart failure since January 23, 1956. However, her condition did not improve with treatment, and dyspnea remained intractable. When she was seen with her attending physician on January 27, 1956, the following note was made: "A large part, if not all, of this patient's dyspnea is undoubtedly due to the free fluid in both pleural cavities, demonstrable today on physical examination." The chest x-ray, taken on January 24, 1956 (figure 7), was reported as showing "cardiac enlargement and pulmonary congestion." Pleural fluid was not mentioned. Thoracentesis on January 27, 1956 yielded 700 ml. of amber-colored fluid from the right pleural cavity, and 600 ml. from the left, with immediate disappearance of the patient's dyspnea, and dramatic return of complete comfort and relaxation. Eventual recovery from the congestive heart failure was complete.

Case 13. A 64 year old man with chronic coronary heart disease and pulmonary emphysema was being treated in the hospital with a low salt diet, bed-rest, digitalis and Mercuhydrin for marked dyspnea, restlessness, insomnia and cough, which were attributed to left heart failure. These symptoms, however, remained intractable to therapy. On examination on October 7, 1953, the patient was markedly dyspneic and restless. The chest was emphysematous in contour, and bronchitic squeaks and rhonchi were audible throughout both lungs. Impairment of resonance was detected in the lowermost portion of the right chest posteriorly, extending upward from the costal arch to the level of D 9, and breath sounds were diminished in this region. The liver edge was palpable three fingerbreadths below the right costal margin, and a small amount of ascitic fluid was thought to be present. There was no peripheral edema. The chest x-ray taken on October 7 (figure 8) was reported as showing "a bilaterally disseminated infiltrative process, accentuated in the midlung fields, and associated with peripheral and hilar nodes. Differential diagnosis cannot be made from the x-ray alone between neoplasm, tuberculosis, edema, pneumonitis, sarcoidosis, fibrosis, or fungus disease. The right costo-phrenic angle and posterior costo-phrenic sinus on the lateral view are slightly obscured, possibly signifying a very small pleural effusion."

After physical examination and review of the x-ray, the following note was made: "The intractable dyspnea and marked restlessness to the point of refusal of oxygen inhalation by any method of administration are very likely caused by a right pleural effusion, the extent of which although obscured somewhat by emphysema, is greater on physical examination than in the x-ray, in which only minimal pleurisy is present, and the clinical effect of which may be greater than the apparent amount may be considered to warrant."

Immediate right thoracentesis yielded 800 ml. of light amber fluid, with immediate and total relief of the marked dyspnea, restlessness and pleuritic pain. The

patient was at once able to lie flat on his back without discomfort.

Subsequently, complete recovery took place, with resolution of all shadows in the x-ray. An etiologic diagnosis was never definitely established.

Comment: In this case, medical attention was focused on the widely disseminated infiltrative process in both lungs in the x-ray. The minimal impairment of resonance in the lower right chest either was not noted, or was disregarded completely as being of no moment in comparison with the extensive pulmonary disease in causing the patient's dyspnea and orthopnea.

The minimal degree of pleurisy in the x-ray was considered to be of no significance. The final additive effect of the small pleural effusion was not recognized, and the immediate and complete relief of the dyspnea and other symptoms was a surprise to the attending physician and roentgenologist. In addition, the respectable amount of fluid obtained, with the minimal physical and x-ray findings, was also unexpected. This case illustrates the fact that x-ray cannot be relied upon to indicate the amount of fluid present or the clinical significance of a small effusion; nor can it be used as the sole or even an important indication as to the necessity or advisability for diagnostic and therapeutic thoracentesis. The removal of this small amount of fluid was not only of great symptomatic benefit, but was also definitely the instantaneous turning point in this patient's illness, and the beginning of his recovery.

# B. True Depth of the Costophrenic Gutter Not Apparent Until After Thoracentesis or Spontaneous Resolution of Hydrothorax

Case 14. A 63 year old woman with chronic bronchial asthma, pulmonary emphysema and arteriosclerotic and hypertensive heart disease entered the hospital in cardiac failure on December 2, 1956, with complaints of dyspnea, orthopnea, cough and ankle edema. On December 19, 1956, severe dyspnea and restlessness developed in spite of prolonged therapy for cardiac failure. Examination disclosed cardiac enlargement, a loud apical systolic murmur, atrial fibrillation, and bilateral dullness and diminished breath sounds in the chest below the level of D 10 posteriorly. Bilateral thoracentesis was done, with removal of 550 ml, fluid from the right pleural cavity and 450 ml, from the left, with complete relief of the dyspnea (figure 9). Figure 8 is also an example of this point.

# C. Pleural Fluid Diagnosed as Pneumonia

Case 15. An 84 year old man with a barrel chest was seen on January 2, 1951, with the history of sudden onset of a chill, cough, dyspnea and restlessness the previous day, at which time dullness on percussion over the right lower lobe led to a diagnosis of pneumonia by his physician and the patient was hospitalized. However, there had been gradual increase in restlessness, cyanosis, air hunger and stupor. X-ray of the chest disclosed "a shadow in the R.L.L. probably due to pneumonia."

On physical examination, the percussion note over the lower half of the right chest was flat rather than dull. Thoracentesis of the right pleural cavity evacuated 1,800 ml. of straw-colored fluid, with immediate relief of dyspnea. All abnormal

physical signs over the right chest disappeared with removal of the fluid.

# D. Overlying Soft Tissues Obscure Costophrenic Angles

Case 16. A 66 year old woman was seen on May 14, 1955, with a history of shortness of breath and swelling of the ankles of three weeks' duration, and several previous hospital admissions for congestive heart failure. On May 16, 1955, x-ray of the chest was reported as showing "hypertensive heart disease; pulmonary congestion; the costo-phrenic angles cannot be evaluated because of the overlying soft tissue." The patient did well for three days on treatment for congestive heart failure. On May 17, 1955, she became acutely dyspneic again. Dullness on percussion was elicited over the right base posteriorly. On May 18, 1955, a right thoracentesis evacuated 650 ml. of clear yellow fluid, with marked relief of the dyspnea.

# E. "Pleural Reaction"; "Pleural Thickening"

Case 17. In the case of a 65 year old man with repeated hospital admissions for chronic congestive heart failure, the following note was made on September 7, 1946: "Degenerative heart disease with failure is the more intractable because of the marked pulmonary emphysema. There is free fluid in the right pleural cavity on physical examination, and this may be the main cause, in the presence of heart failure and associated pulmonary emphysema, of the patient's dyspnea."

November 1, 1946 (on another hospital admission), report of a chest x-ray taken on this day read: "In the right base we see evidence of an old *pleuritic thickening* involving the diaphragm and ascending along the lateral thoracic wall." Exploratory thoracentesis of the right chest, performed a few hours later on the same day, yielded

2,000 ml. of clear yellow fluid!

# IV. Miscellaneous Observations on Pleural Effusions in General, Large and Small

A. Pleural Fluid and Acute Pulmonary Edema. In the presence of heart failure, hydrothorax may present itself with the clinical picture of intractable or frequently repeated attacks of acute pulmonary edema, which may not be relieved until the pleural fluid is removed by thoracentesis. Indeed, the mechanical removal of pleural fluid, when present, may be the only means of permanently relieving the pulmonary edema. While these two conditions are due to the same underlying pathologic process (of heart failure), and their simultaneous appearance could be coincidental and mutually unrelated, the rapid and complete disappearance of the objective signs of pulmonary edema after thoracentesis, and only after thoracentesis, indicates a direct causal relationship between the two. The hydrothorax acts as an added load on the disabled and functionally inefficient heart and lungs to precipitate or perpetuate failure and pulmonary edema. The continued presence of hydrothorax prevents response to the usual medical measures for heart failure; with removal of the hydrothorax, acute failure subsides at once. Thus hydrothorax not only is an effect, but may also in turn become a cause of persistent heart failure and pulmonary edema.

It is unfortunate that, all too frequently, attention is focused completely on the obviously present state of acute pulmonary edema, and the dyspneic emergency attributed entirely to this, though the usual medical measures for this condition proved ineffectual, even until the death of the patient. Often the posterior aspects of the chest are not even examined in the critically ill patient, who is usually in the decubitus or orthopneic position; and the moist râles of pulmonary edema, audible on the anterior aspects and in the axillae, are *assumed* to be the only abnormal physical findings present posteriorly also. If the back is examined and basal dullness is found, it may be attributed to dependent pulmonary edema fluid; or, if the presence of hydrothorax is recognized, the amount may be underestimated, or its causative role in precipitating or perpetuating refractory pulmonary edema not recognized.

In short, acute pulmonary edema, when present, and especially when refractory to the usual medical management of this condition, cannot be accepted uncritically as the sole cause of a dyspneic emergency in the presence of heart failure, but should serve as an indication for a careful examination of the postero-inferior aspects of the chest for the presence of hydrothorax; if this be demonstrated, then removal by thoracentesis is indicated immediately, even if the amount seems small.

Case 18. A 75 year old woman with a history of acute myocardial infarction three years previously, and repeated episodes of cardiac failure and pulmonary edema since then, was seen with her family physician while in another episode of acute pulmonary edema on June 26, 1950. She had not responded to routine medical treatment for congestive heart failure during the previous three weeks in the hospital.

Examination revealed a comatose patient, severely dyspneic and cyanotic, with imperceptible pulse and blood pressure. The chest was huge and barrel-shaped. The heart was enlarged to the left, with an apical systolic murmur. Bubbling râles and rhonchi were audible throughout both lungs, with impaired resonance on per-

cussion over both pulmonary bases below the level of D9 posteriorly.

of the acute pulmonary edema disappeared at once.

With the administration of oxygen by mask, and digitoxin, aminophylline and atropine intravenously, the patient improved somewhat. The pulse became perceptible at a rate of 160, and presented the completely irregular rhythm of auricular filbrillation. The blood pressure gradually rose to 110 systolic. Thoracentesis of the left chest now yielded 1,000 ml. of blood-tinged amber fluid, with considerable improvement in the dyspnea, return of consciousness, and slowing of the pulse rate to 120. The following day, thoracentesis of the right chest yielded 1,100 ml. of straw-colored fluid, with complete relief of dyspnea and almost immediate disappearance of all of the moist pulmonary râles. Subsequent recovery on continued medical management for heart failure was uneventful. No further thoracentesis was necessary.

Case 19. A 70 year old woman was admitted on July 1, 1951, as an acute emergency, in shock, with imperceptible pulse and blood pressure, severe precordial pain, sweating, dyspnea, wheezing, rhonchi, coarse moist râles throughout both lungs, and impaired resonance over the right lung base posteriorly up to the level of D 8. The chest was emphysematous in contour. The diagnosis was acute myocardial infarction, left ventricular failure, acute pulmonary edema, and right hydrothorax. Treatment for acute heart failure and pulmonary edema was instituted. The next morning the state of shock had disappeared, but dyspnea, restlessness and generalized moist pulmonary râles persisted. Thoracentesis of the right chest yielded 850 ml. of straw-colored fluid, and completely relieved the dyspnea and restlessness. The moist râles

Case 20. A 65 year old woman with an emphysematous chest and arteriosclerotic heart disease had been in the hospital for six weeks with persistent heart failure and repeated attacks of pulmonary edema. She was seen with her family physician while in an attack of acute pulmonary edema on September 27, 1951. She was extremely dyspneic, although in an oxygen tent. Examination disclosed the heart enlarged to the left, with an apical systolic murmur. Flatness to percussion and absent tactile fremitus and breath sounds were elicited over the right chest posteriorly below the level of D 9. Emergency thoracentesis of the right pleural cavity yielded 900 ml. of straw-colored fluid, with immediate and spectacular relief of the dyspnea, and complete disappearance of the moist pulmonary râles. The patient was relaxed and comfortable for the first time since the onset of dyspnea six weeks previously.

Case 21. A very obese 47 year old man with emphysema and diabetes mellitus suffered an acute anterior myocardial infarction on May 29, 1953. He did well at

bed-rest in the hospital until June 9, 1953, when, at 2 a.m. (with no previous premonitory symptoms or dyspnea on the preceding day), he awakened suddenly with marked dyspnea, wheezing, apprehension, violent restlessness, air hunger, tachycardia and cyanosis, not relieved by two doses of Demerol and an oxygen tent. When seen at 3 a.m., the patient had tossed aside the canopy of the oxygen tent and was sitting up in bed, wild-eyed with dyspnea and apprehension, breathing noisily, wheezing, and tossing about in bed. Cursory rapid examination disclosed expiratory rhonchi, wheezing and moist râles diffusely in both lungs, and flatness on percussion over the lowermost portions of the posterior aspect of the chest up to the level of D 8 on the right and D 9 on the left. Immediate thoracentesis of the right pleural cavity yielded 1,450 ml. and of the left, 1,100 ml. of straw-colored fluid (total of 2,550 ml.), with complete relief of all symptoms and abnormal physical findings. The patient now sat up comfortably in bed, talking volubly and cheerfully, smiling, laughing and joking as if he had never been ill. Digitalis and Mercuhydrin were ordered. The next day he remained much improved, with a regular pulse of 104 per minute. On June 11, 1953, a good diuresis from Mercuhydrin was recorded. On June 15 he was able to lie flat in bed without dyspnea. The pulse rate was 84. Subsequently the patient was discharged from the hospital in good condition.

Case 22. A 66 year old man with arteriosclerotic heart disease and episodes of acute pulmonary edema in the past was seen with his physician on January 8, 1953. Progressively increasing dyspnea in the last three months had terminated in an attack of acute pulmonary edema the previous day, for which the patient had been hospitalized and treated with Demerol, aminophylline, oxygen under positive (ex-

piratory) pressure, and intramuscular Mercuhydrin.

Examination disclosed a dyspneic and orthopneic patient receiving oxygen by mask; pulse, 84 and regular; blood pressure, 130/80 mm. of Hg in both arms; jugular engorgement; cardiomegaly to the left, with an apical systolic murmur; emphysematous chest contour with bronchitic wheezes and moist râles audible diffusely in both lungs; flatness on percussion, absent fremitus and breath sounds over the lower third of the right chest posteriorly and in the axilla; and hepatomegaly. There was no peripheral edema.

Thoracentesis of the right pleural cavity yielded 1,000 ml. of a straw-colored fluid, with immediate relief of the dyspnea and all other symptoms. Only occasional

scattered moist râles were audible in the lungs one hour later.

Case 9 is also an example of this type.

B. Pleural Fluid and Mental Symptoms. Asphyxia and cerebral anoxia produced by pleural fluid (alone, or as a final increment in a combination of factors such as we have been discussing) may precipitate mental symptoms and psychosis (particularly in middle aged or elderly individuals) which are relieved by thoracentesis.

Case 23. A 68 year old woman was seen in her home, with her son, the referring physician, late on the night of December 2, 1944. She had suffered from hypertension and arteriosclerotic heart disease for years, and in the last year had been a bedridden invalid. Mental symptoms of hallucinatory and delusional nature had been present for several weeks, and the patient was scheduled to be admitted to a mental institution in a few days. In the last three weeks, dyspnea and syncopal attacks had also been present.

On examination, the patient was lying in marked orthopneic position, receiving pure oxygen by mask. The jugular veins were dilated. The chest was thin but emphysematous in contour, with increased anteroposterior diameter. Slight but definite impairment of resonance and diminished breath sounds were elicited over the lower portions of both sides of the chest posteriorly, extending up to the level of D 8. The percussion note was not flat, however, because of the associated

emphysema.

The patient was hospitalized. Thoracentesis of the right chest yielded 1,500 ml. of straw-colored fluid. The next day, 1,200 ml. of fluid were obtained on thoracentesis of the left chest. Thereafter the patient's breathing and mentality were much improved. On December 8, 1944, she was able to sit up comfortably in bed; breath sounds were clearly audible in both bases posteriorly. Two days later, 800 ml. of fluid were removed from the left pleural cavity, and the following day, 600 ml. from the right. On this day the patient was sent home on therapy for congestive heart failure, without dyspnea, comfortable, and completely rational. She remained mentally clear until her death from a cerebrovascular accident four years later.

Case 24. A woman, age 70, was seen in a medical ward in the hospital to which she had been admitted on February 15, 1954, with symptoms and signs of congestive heart failure due to arteriosclerotic heart disease. Since admission she had been completely psychotic, irrational, disoriented, and alternately delirious and stuporous, particularly at night, when her noisy outcries and symptoms of terror in spite of heavy sedation disturbed the entire ward. Psychiatric consultations had been requested on February 23, 1954, with a view of transferring the patient from the

medical to a psychiatric ward.

In a preliminary discussion with members of the resident staff, before examination of the patient, the relationship of pleural fluid in heart failure to asphyxial dementia, as demonstrated in the preceding case, was pointed out, and the possibility was suggested that relief of anoxia by removal of pleural fluid, if found, might restore

the patient's sanity. Of this the staff were extremely skeptical.

On examination, the patient was dyspneic, orthopneic, and in the mental state described. The jugular veins were distended. The chest was emphysematous. Flatness on percussion and absent breath sounds were demonstrated below the level of D 9 on the right side. (The back had not been examined recently because "heart failure" was deemed to be a sufficient explanation of the patient's dyspnea, even though she had not responded to cardiac management.)

Thoracentesis yielded 1,000 ml. of straw-colored fluid, with immediate (although not complete) relief of the patient's dyspnea. She became much quieter, even at night, and in a few days both cardiac failure and mental aberration had completely disappeared. She ultimately left the hospital without dyspnea and mentally clear.

Case 25. A 50 year old man with arteriosclerotic heart disease and congestive failure was seen as an emergency on April 19, 1949. Examination revealed a dyspneic patient, irrational, disoriented and psychotic. The chest was emphysematous in contour. Impairment of resonance and diminished to absent breath sounds were detected below the level of D 10 on the right side of the chest posteriorly. Thoracentesis yielded 1,000 ml. of straw-colored fluid, with relief of the dyspnea. The following day the patient was much improved and mentally clear.

Case 26. A 77 year old man with arteriosclerotic heart disease and repeated attacks of acute pulmonary edema in the recent past was seen on December 10, 1953, comatose and apparently in terminal condition, with severe dyspnea, cyanosis and air hunger. Moist râles and rhonchi were audible diffusely throughout both lungs. Slight impairment of resonance and diminished breath sounds were elicited over the right side of the chest posteriorly below the level of D 10, and were interpreted as

being suggestive of a small amount of free pleural fluid.

Exploratory thoracentesis of the right pleural cavity (with the needle in the eleventh interspace, and the patient on his left side elevated to the semi-sitting position on a back rest) yielded 900 ml. of a straw-colored fluid, with immediate improve-

ment in the patient's color and breathing. Within a few minutes he emerged from the comatose state and talked rationally with his son.

Comment: These cases clearly demonstrate that mental and cerebral symptoms of asphyxial origin which develop in the presence of cardiac failure are frequently due to associated hydrothorax, and are relieved when (and only when) the pleural fluid is removed by thoracentesis. The mental symptoms may be the presenting or most prominent part of the clinical picture. Such cases, particularly in the middle aged or elderly, are often carelessly misdiagnosed "senile" or "toxic" dementia, with potentially embarrassing and serious consequences. The development of mental symptoms in dyspneic patients with heart failure (if cerebral effects of the various medicaments used therapeutically can be excluded) should lead to a careful search for pleural fluid, and this, if found, should be removed mechanically as a therapeutic test, even if apparently small in amount.

C. Digitalis Intoxication. Intractability and lack of response to the usual medical management of congestive heart failure in the presence of unrecognized pleural fluid—with persisting symptoms of dyspnea, orthopnea, cyanosis, cough, restlessness, rhonchi, wheezing, and moist pulmonary râles—frequently lead to excessive administration of digitalis and resulting clinical and electrocardiographic evidences of digitalis intoxication. The situation is similar to that which often obtains with other easily overlooked underlying etiologic factors of intractable heart failure, such as high-grade mitral or aortic stenosis; masked hyper- or hypothyroidism; pericardial effusion or adhesive pericarditis; beriberi or amyloid heart disease; acute myocarditis, etc., etc. Intractable heart failure, then, and resulting digitalis intoxication, should indicate a careful search for pleural fluid, and its removal mechanically if found, even if apparently small in amount.

D. Breathlessness and Refusal of Oxygen. Although dyspnea is a common and expected symptom in cardiac failure, disproportionate and prolonged dyspnea in spite of otherwise adequate medical therapy, and continuous or paroxysmal breathlessness, must always lead first to consideration of possible pleural fluid and to a careful search for this. Removal of pleural fluid when found, even when small in amount, may lead to complete relief of dyspnea and breathlessness; more important, mechanical removal of fluid may be the only means of relieving dyspnea and starting intractable heart failure on the road to recovery.

A characteristic symptom in some cases of extreme dyspnea and air hunger due to pleural fluid is the refusal of oxygen by any avenue of administration, the patient tearing the mask from the face, pulling the catheter out of the nose, or tossing aside the canopy of the oxygen tent. With this he frequently sits up in bed in wild excitement, tossing his body about, flailing his arms, and gasping for breath, often motioning to have the windows opened wider to admit more air. The refusal of oxygen is no doubt in part

a manifestation of the extreme asphyxial restlessness, and claustrophobia on application of the face mask; but in part also may represent an instinctive physiologic recognition by the patient of the fact that, under the circumstances, the oxygen therapy is not providing significant or adequate relief of the anoxia and dyspnea. It must be emphasized again that extremely severe dyspnea of this type may be caused by relatively small amounts of fluid, and be completely relieved by their removal.

- E. Sudden Onset of Acute Dyspnea Due to Pleural Fluid. Acute dyspnea due to pleural fluid (again, as the final increment in a combination of factors) may appear suddenly (almost instantaneously), and frequently at night, even though presumably the fluid has been accumulating gradually over a period of days. It is as if a critical level has to be reached before the condition of air hunger is triggered. This phenomenon is illustrated in cases 21 and 27.
- F. Rapidity of Formation of Pleural Fluid in Heart Failure. The rate at which hydrothorax fluid may be formed in the presence of heart failure is not well documented. We have seen one case where 1,500 ml. of fluid recurred in one pleural cavity within a six-hour period (and similar amount may have occurred de novo in the other pleural cavity).
- Case 27. A 46 year old diabetic male with acute myocardial infarction, pulmonary edema and intermittent shock of 36 hours' duration was seen with his physician at 11 p.m. on May 14, 1952. Violent restlessness and air hunger were manifest. The chest was emphysematous in contour. Flatness on percussion and absent breath sounds were elicited over the lower thirds of both sides of the chest posteriorly. Rapid thoracentesis yielded 1,200 ml. of straw-colored fluid from the right pleural cavity, all of the fluid obtainable being removed; percussion resonance was unimpaired down to the costal arch after the procedure, and breath sounds came through clearly. Thoracentesis of the left pleural cavity in three separate sites yielded no fluid.

Improvement in the patient's condition and in the relief of dyspnea was immediate and spectacular. He was quiet, comfortable and relaxed, sat up in bed and lay down at will without effort, talked easily, smiled and laughed, and then fell into a relaxed and comfortable sleep.

The patient slept quietly all night. At 6 a.m. he awakened with sudden recurrence of air hunger, and died within two hours. Autopsy disclosed thrombotic occlusion of the left coronary artery, extensive anterior myocardial infarction, and marked generalized coronary arteriosclerosis. There were 1,500 ml. of fluid in each pleural cavity!

G. Repeated Re-accumulation. Episodes of re-accumulation of pleural fluid may occur with or without overt heart failure (or when all other evidences of heart failure have responded to the usual medical measures for this condition and disappeared), or following myocardial or pulmonary infarction, and may require repeated periodic aspiration at intervals of days or weeks. After several such aspirations, pleural fluid may disappear permanently; but in some cases recurrence may continue indefinitely, with a

fatal outcome. In one case, a man 60 years of age who had had an acute myocardial infarction, recurrences of left-sided hydrothorax requiring eight successive aspirations (from 1,200 to 1,400 ml. at intervals of from four days to two weeks), in spite of continual bed-rest, low salt diet, digitalization and mercurial diuretics (with good diuretic effect), occurred in a three-month period, with final fatal outcome. An interesting feature in this case was the fact that the earliest evidence of re-accumulation of fluid (except for the development of dyspnea) was the appearance of distant bronchial breath sounds below the level of D 10 over the left chest posteriorly on auscultation (Baccelli's phenomenon), when the amount of fluid present was still small. Portable chest x-ray immediately after tapping on one occasion showed the left pleural space to be free of fluid, and the underlying left lung to be completely normal.

H. Urgency of Tapping. When severe dyspnea, continuous or intermittent, is associated with pleural fluid, the mechanical removal of the fluid becomes an immediate indication, since a delay of minutes, hours or days may result in fatal asphyxia. We have seen fatal cases in which, based on the experiences herein described, it might be reasonably assumed that timely

thoracentesis might have prevented a fatal outcome.

Speaking generally, one may say that it is perhaps the best part of wisdom to test the suspicion of free pleural fluid (based on physical or x-ray findings) by exploratory thoracentesis, even when mild or moderate dyspnea is a feature of heart failure or extensive pulmonary disease. While it is true that most small or moderate effusions will subside on expectant and medical management alone, in a given case one cannot be sure whether this will occur, or whether sudden, severe asphyxia will develop and prove fatal before thoracentesis can be done. Even when it is likely that favorable resolution will occur on medical management alone, early mechanical removal of the fluid hastens relief of dyspnea, improves clinical response to cardiotonic and diuretic medication, shortens the course of illness, and allays apprehension in the attending physician's mind. Certainly in the presence of severe dyspnea, continuous or intermittent, thoracentesis cannot be delayed pending a trial of slow and unpredictable medical management. Especially at night, the temptation is great on the part of a sleepy house officer or attending physician to treat an attack of suddenly aggravated dyspnea with a telephone order for an injection of an opiate (which may be harmful) and oxygen inhalation (which is not effective under these circumstances), and even when pleural fluid is recognized as the cause of the dyspnea, to delay thoracentesis until morning, by which time the patient will often have died.

While we have been impressed with (and stressed in this paper) the benefit that may result from timely aspiration of small pleural effusions in cases of refractory heart failure, it goes without saying that such benefit does not occur invariably. Cases occur where the degree of heart failure

and associated pulmonary disease is so severe that aspiration of a small effusion may cause no—or only transient—improvement. This in no way condones the failure to test the effect of such aspiration, however, since only therapeutic thoracentesis can prove this point in any given case, and salvage such cases as we have described here.

## SUMMARY AND CONCLUSIONS

1. A relatively small pleural effusion may precipitate a critical degree of dyspnea and air hunger and even cause death, in the presence of antecedent cardiac and pulmonary disease which already seriously interferes with pulmonary function and causes difficulty in breathing. As little as 500 ml. may be of significance in this regard.

2. This situation occurs most commonly in middle aged or elderly individuals with coexistent congestive heart failure and pulmonary emphysema or fibrosis; but a summation of other pathologic processes in the lungs (infarction, pneumonia, atelectasis, etc.) in the presence of heart disease or failure may similarly enhance the final asphyxial effect of a small increment of pleural fluid.

3. Recognition and mechanical removal of a small pleural effusion by thoracentesis under these circumstances provide great palliative benefit, and

are frequently lifesaving.

4. Dogmatic and axiomatic statements that, in all cases, pleural fluid is not to be tapped unless the upper level reaches a certain arbitrary point (such as the angle of the scapula) condemn many patients to needless suffering and death.

- 5. Diagnosis of a small effusion in the presence of heart failure and emphysema may be difficult. It is based mainly on a high index of suspicion that any degree and extent of impairment of resonance in the lowermost portions of the posterior aspects of the thoracic cage may be due to pleural fluid; and the free use of exploratory puncture, properly performed, to test this suspicion.
- 6. Chest x-ray is frequently misleading and not reliable. Significant amounts of pleural fluid (500 to 1,000 ml.) may not be detected in the posteroanterior view at all, or may appear merely as "blunting," "obliteration" or "haziness" of the costophrenic angle.
- 7. The presenting clinical picture is frequently that of acute pulmonary edema, which obscures the diagnosis of pleural fluid, and is relieved only when the pleural fluid is removed by thoracentesis.
- 8. "Refractory heart failure," and digitalis intoxication due to overmedication, occur commonly due to unrecognized pleural fluid.
- 9. Violent restlessness (refractory even to massive doses of sedatives and opiates), inexplicable breathlessness, extreme dyspnea, and refusal of oxygen therapy by any avenue of administration, are common symptoms

of hidden pleural fluid under the circumstances being discussed, and are relieved at once by thoracentesis.

10. Mental and cerebral symptoms simulating—and often mistakenly diagnosed as—senile or toxic psychosis may be caused by asphyxia due to pleural fluid, and be relieved only after thoracentesis.

11. Early thoracentesis is indicated when any degree of hydrothorax in cardiac failure is associated with a significant degree of dyspnea.

### SUMMARIO IN INTERLINGUA

Un relativemente micre effusion pleural-ordinarimente considerate como disproviste de signification clinic-pote nonobstante precipitar un grado critic de dyspnea e de "fame de aere" e mesmo ager como causa de morte in le presentia de antecedente morbo cardiac e pulmonar le qual jam interfere in le function pulmonar e causa difficultates de respiration. Un quantitate de solmente 500 ml pote esser significative. Iste situation occurre le plus communmente in subjectos de etate medie o avantiate con coexistente congestive disfallimento cardiac e emphysema o fibrosis pulmonar. Sed un summation de altere processos pathologic in le pulmonesinfarcimento, pneumonia, atelectasis, etc.-es similemente capace, in le presentia de morbo o disfallimento cardiac, a promover le ultime effecto asphyxial de un micre augmento del liquido pleural. Le recognition e le elimination mechanic de un micre effusion pleural per thoracentese provide sub iste conditiones un grande beneficio palliative e es frequentemente lo que salva le vita del patiente. Le assertion dogmatic e axiomatic que le extraction de liquido pleural non debe unquam effectuar se ante que un certe nivello arbitrari, per exemplo le angulo del scapula, es attingite ha condemnate plus que un patiente a innecessari suffrentias e al morte. Le diagnose de un micre effusion in le presentia de disfallimento cardiac e emphysema es frequentemente difficile. Illo se basa primarimente super un alte indice de suspicion que omne grado e omne extension de vitiation del resonantia in le portiones le plus inferior del aspectos posterior del thorace es possibilemente causate per liquido pleural e super le libere uso de puncturas exploratori, appropriatemente effectuate, pro verificar ille suspicion. Roentgenogrammas thoracic es frequentemente deceptive e non es digne de confidentia. Il es possibile que quantitates significative de liquido pleural -500 o 1.000 ml-escappa completemente al detection in un exposition anteroposterior, o illos se manifesta solmente como un "obfuscation", "oblitteration", o "nebulation" del angulo costo-phrenic. Le tableau clinic de presentation es frequentemente un tableau de acute edema pulmonar le qual obscura le diagnose de liquido pleural e es alleviate solmente quando le liquido pleural es eliminate per thoracentese. "Disfallimento cardiac refractori" e intoxication digitalic per hypermedication occurre communmente in consequentia de non-recognoscite liquido pleural. Violente disquietude-refractori mesmo a massive doses de sedativos e opiatos-si ben como inexplicabile manco de halito, extreme dyspnea, e rejection de therapia a oxygeno per non importa qual via de administration es symptomas commun de occulte liquido pleural in situationes del typo hic discutite, e illos es promptemente alleviate per thoracentese. Symptomas mental e cerebral que simula psychosis senil o toxic e que es-in multe casos-diagnosticate erroneemente como tal pote esser causate per asphyxia in consequentia de liquido pleural e se allevia solmente post le effectuation de thoracentese. Thoracentese precoce es indicate quando non importa qual grado de hydrothorace in disfallimento cardiac es associate con un grado significative de dyspnea.

Le autor cita 27 casos in illustration del supra-presentate argumentos.

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# CASE REPORTS

# NEPHROPATHY OF POTASSIUM DEPLETION: REPORT OF A FATAL CASE \*

By Wu-Hao Tu, M.D., † CARROLL C. Jones, M.D., ‡ and MAX S. ALLEN, M.D., F.A.C.P., Kansas City, Kansas

THE effects of potassium depletion on the structure and function of the kidneys have probably been observed for at least 40 years. In 1919 Jaffé and Sternberg 1 described vacuolar degeneration of the renal tubules in patients who died of dysentery. These observers suggested that the lesion was a distinct pathologic entity, perhaps associated with intestinal disease. Deficiency of potassium as a cause of such renal lesions was suggested by Perkins et al.<sup>2</sup> and by Luft et al.3 The subject has recently been well reviewed by Relman and Schwartz, 4, 5, 6 who confirmed the etiology and pathogenesis of the lesion by a series of studies with renal biopsy and renal function tests, and by measuring potassium balance in patients showing potassium depletion from chronic intestinal disorders. They suggested that the nephropathy of potassium depletion is a distinct clinical and pathologic entity.

· The renal lesions of potassium deficiency are confined chiefly to the tubular epithelium. In man the change is primarily vacuolization of the tubular epithelium, and is limited to the convoluted tubules. In rats a hyperplastic obstructive lesion appears in the collecting system which leads to secondary dilatation. degeneration and necrosis in the proximal tubule.4 The most consistent dysfunction of the kidney in potassium depletion nephropathy is pitressin-resistant isosthenuria, a tubular malfunction. The glomerular filtration rate is often reduced in diarrhea-induced potassium deficiency, but generally has not been considered to be of significance in the reported cases.5

The purpose of this communication is to report a patient who died in uremia, and whose clinical picture and pathologic findings are consistent with the diagnosis of nephropathy due to potassium depletion. Although fatal cases have not previously been reported, it appears that renal failure with fatal outcome may ultimately occur in severe potassium depletion.

#### CASE REPORT

A 52 year old unmarried white woman was admitted to the University of Kansas Medical Center on September 22, 1958, and died four days later. She was unable

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to give a lucid history, but from relatives it was learned that she had worked in her usual capacity as a cashier in a department store for 20 years until four days before admission. She had noted increasing dyspnea on exertion, and orthopnea for three days, and had been lethargic for 12 hours before admission. There was general agreement among her relatives that her diet had been grossly inadequate for many years, and that she had been a habitual user of various laxatives in large doses for 20 years. She took aloin and phenolphthalein laxatives of various types, commonly taking a dose of such medication after each meal, and insisted on having a stool at

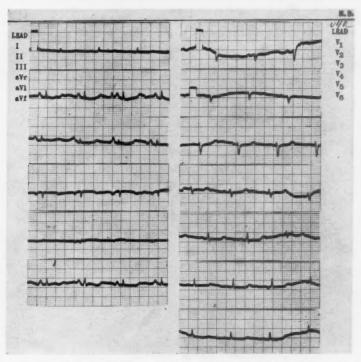


Fig. 1. Electrocardiogram, September 24, 1958, showing increased amplitude of P waves and evidence of hypokalemia.

least twice daily. Her stools were usually watery, and if she failed to have a stool after a laxative she would use a tap water enema. Her diet apparently consisted largely of breadstuffs, ice cream and soft drinks, and contained little meat or fruit.

The patient's past history, obtained from the relatives and from hospital records elsewhere, revealed that she had undergone thyroidectomy for a nodular goiter in 1947. There was no history to suggest thyrotoxicosis. In 1952 she had had a second thyroidectomy for the removal of a "slowly growing fetal adenoma of the thyroid." At that time she had weighed 87 pounds and measured 61 inches in height. The urine at that time (1952) was acid in reaction and negative for albumin, sugar and acetone. The sediment had shown 2 to 4 white blood cells and many mucus threads per high power field. Blood sugar and nonprotein nitrogen were within normal

limits. The patient had had the usual childhood diseases, and was reported to have had scarlet fever at age 36 years, and "jaundice" at age 37. There was a family

history of thyroid disease. Examination revealed a small, cachectic white woman who was restless and

somewhat lethargic. She responded very slowly to questions, and at times gave incoherent answers. The blood pressure was 76/58 mm. Hg; pulse, 72 and regular; respiration, 30 per minute; temperature, 97.7° F. There was a moderate degree of exophthalmos. The pupils and optic fundi appeared to be normal. The thyroid gland was not palpable. The thorax was emphysematous in appearance and hyperresonant to percussion, and the respiratory excursions were greatly diminished. Scattered rhonchi were heard. There was marked venous distention in the neck and upper extremities, even with the patient sitting at 50°. Examination of the

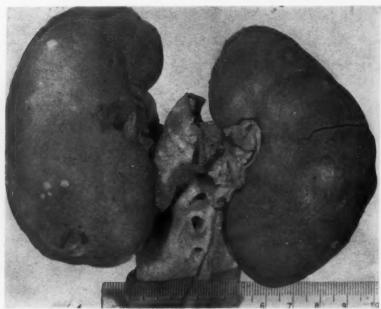


Fig. 2. Swollen kidneys. Cortical surface shows benign tubular adenomas and retention cysts.

abdomen revealed no abnormalities. There were marked muscular wasting of the entire body and clubbing of the fingers and toes. No edema or cyanosis was noted. The tendon reflexes were absent, there was no Babinski sign, and the cranial nerves seemed to be intact, although sensory modalities could not be adequately evaluated.

On admission a blood count showed: hemoglobin, 11 gm.%; hematocrit, 35%; white blood cells, 18,400/cu. mm., with 93% polymorphonuclear cells, of which 37% were nonfilamented; 6% lymphocytes, and 1% eosinophils. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was nonreactive. On the morning following admission the blood urea nitrogen was 114; creatinine, 7.9, and glucose, 113 mg. per 100 ml. The plasma CO<sub>2</sub> combining power was 8.8; serum sodium, 127; potassium, 1.8; chloride, 94; calcium, 3.4 mEq. per liter. The serum inorganic phosphorus was 15.5 mg. per 100 ml.; serum alkaline phosphatase, 1.76 mM units per liter; cholesterol, 294 mg. per 100 ml., with 55% cholesterol esters. The venous pressure was 198 mm. of normal saline. Blood ammonia 25 two days after admission was 61.3 µg. per 100 ml.\* Two hundred milliliters of urine obtained at this time by catheterization showed a specific gravity of 1.013, an acid reaction, 2 plus albumin, a small quantity of amorphous crystals, a few epithelial cells, many red cells, and four to six pus cells per high power field. Culture of the urine produced a heavy growth of a proteus species, *Escherichia coli* and enterococci. This was the only urine obtained during the four days of observation. A roentgenogram of the chest revealed a granular, fibrotic type of infiltrative pattern distributed throughout the lungs, and decalcifica-



Fig. 3. Cross-section of right kidney, showing reduced thickness of cortex, prominent corticomedullary junction and small retention cysts in cortex and medulla.

tion of the skeletal structures, with moderate kyphosis of the thoracic spine. An electrocardiogram revealed peaked P waves, flat T waves with prolonged Q-T intervals, U waves and clockwise rotation (figure 1).

During the first 24 hours the patient remained apprehensive and dyspneic. She became increasingly lethargic, and accepted only small amounts of oral fluid. There were several small, incontinent stools. The clinical impression was acute renal failure of unknown cause, probably vacuolar nephropathy of potassium depletion. The patient was treated with oxygen, intravenous fluids and hydrocortisone, but showed no improvement. On the second and third hospital days, 135 mg. of Metaraminol were administered by intramuscular and intravenous routes over a 32-hour

<sup>\*</sup> Normal values in this laboratory lie between 50 and 110 µg. per 100 ml.

period. Four mg. of Levarterenol were given intravenously over a 90-minute period shortly after the completion of hemodialysis. The patient received a total of 80 mEq. of potassium intravenously. The serum potassium level rose to 7.4 mEq. per liter on September 24. This change was reflected in the electrocardiogram by increased height of the T waves; however, prolonged Q-T intervals remained. On the third hospital day the patient's pupils became dilated and fixed, and she was completely unresponsive. She was given hemodialysis by artificial kidney apparatus. Except for a temporary rise of arterial pressure (to 120 mm. Hg) and a fall of the venous pressure to normal range, there was no evidence of improvement, and she remained in a coma. During the latter course of dialysis, sanguineous fluid was aspirated from the stomach. Serum values following the dialysis were as follows: blood urea nitrogen, 40; creatinine, 3.0 mg. per 100 ml.; sodium, 134; potassium, 5.2;

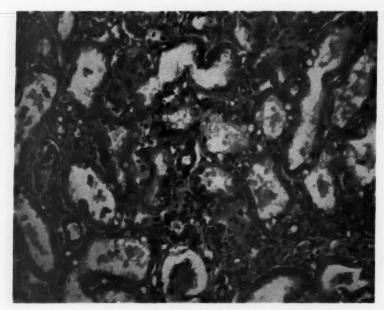
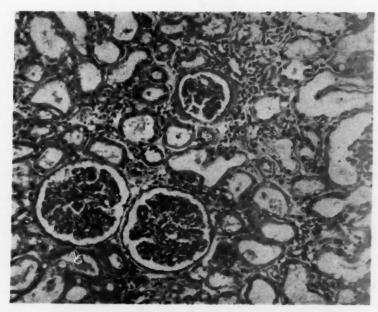


Fig. 4. Cortex of kidney (× 175). Dilated proximal convoluted tubules with clear vacuoles in the epithelial cells. Necrosis and sloughing of some epithelial cells.

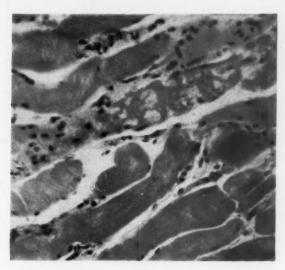
calcium, 5.7; CO<sub>2</sub> combining power, 22.2 mEq. per liter. The blood pressure continued to fall, and the patient died on the following morning, two and one-half hours after completion of hemodialysis.

Autopsy Findings: Autopsy was performed eight hours after death. The body showed marked emaciation; it weighed 61 pounds and measured 60 inches in length. The vertebrae and ribs showed osteoporosis as well as slight osteomalacia. There were several mucosal ulcerations of the upper esophagus, some containing antemortem blood clots, and there were 300 ml. of partially digested blood in the stomach and small bowel. The mucosa throughout the gastrointestinal tract was congested, and in the terminal ileum, cecum and ascending colon there were ragged, acute ulcerations.

The kidneys were of equal size and shape, and were slightly enlarged for a 61 pound woman, the combined weight being 310 gm. The capsules of both kidneys



 $F_{1G}$ . 5. Cortex of kidney ( $\times$  125). Swollen but otherwise normal-appearing glomeruli. Infrequent capsular thickening noted with adjacent interstitial fibrosis. Vacuolar changes in tubular epithelium.



 $Fig.~6.~Myocardium~of~papillary~muscle~of~left~ventricle,~showing~foci~of~myocytolysis~with~lymphocytic~collections~and~interstitial~edema~(<math>\times~410$ ).}

stripped away with difficulty, revealing very finely granular cortical surfaces which contained scattered, shallow depressions, a few retention cysts, and several small, raised, benign tubular adenomas (figure 2). On cut surface the cortex was pallid and reduced in thickness, and the corticomedullary junction was prominent (figure 3). Several small retention cysts were present in the renal papillae as well as in the cortex, and one small calcium oxalate stone was found in a minor calyx of each kidney.

Microscopically, in hematoxylin- and eosin-stained sections, there was marked dilatation of the lumens of the proximal convoluted tubules, and many clear cyto-



Fig. 7. Skeletal muscle, showing swollen fibers with loss of striations and patchy vacuolar changes  $(\times 240)$ .

plasmic vacuoles were seen in the tubular epithelium, chiefly in the proximal convoluted tubules and, to a lesser degree, in the distal convoluted tubules (figures 4, 5). The vacuoles varied in size and location within the cells, being both subnuclear and supranuclear in position. In frozen sections the vacuoles failed to stain with oil red O fat stain or with periodic acid-Schiff (PAS) stain. There was necrosis and sloughing of some tubular epithelium. Hyaline casts were seen in some of the collecting tubules and occasionally in proximal tubules.

While some of the glomeruli showed thickening of Bowman's capsule, the majority showed only slight swelling (figure 5). Moderate fibrosis and scattered

lymphocytes were seen in a few interstitial areas of the cortex, especially beneath the capsule. Von Kossa silver test failed to demonstrate calcium salts, and a careful search for cystine deposits under polarized light did not reveal refractile crystals. The remainder of the urinary tract was not remarkable.

The thyroid gland was absent except for several oval masses of normal appearing thyroid tissue along the lateral margins of the laryngeal cartilage. Although the parathyroid glands were not found by gross dissection, multiple sections of tissue from this region showed a single small bit of hyperplastic parathyroid tissue.

The lungs (combined weight, 1,110 gm.) showed diffuse hyperemia and increased density of the lower lobes. There were 150 ml. of amber fluid in the left pleural space and 300 ml, in the right. Microscopically, a diffuse exudative type of bronchopneumonia involved alveoli of both lower lobes, and the upper lobes showed diffuse emphysema.

The heart weighed 170 gm. A fibrinous pericarditis was present, and there were 60 ml. of cloudy yellow fluid in the pericardial sac. The myocardium of the left ventricle showed generalized interstitial edema and focal areas of myocytolysis with a few chronic inflammatory cells. These latter lesions were most abundant in the papillary muscles (figure 6).

The adrenals (combined weight, 15.6 gm.) were normal by gross and microscopic examination.

Microscopically, striated muscle fibers were swollen, and showed marked focal degenerative lesions, manifested by pale vacuolar changes and a loss of cross striations (figure 7).

Gross and microscopic examination of the brain showed no significant abnormality.

All cultures from both kidneys, the blood of the heart, and the pericardial fluid were negative.

## DISCUSSION

It appears that the vacuolar degeneration and edema of the kidneys were so extensive as to have been the cause of the renal shutdown. There was a persistent hypotension, but no pathologic changes of acute tubular necrosis were found. A serum potassium concentration of 1.8 mEq. per liter in the presence of severe metabolic acidosis indicates that the depletion of body potassium had been even more profound than was apparent from the low serum concentration. It has been established that, in general, a low serum potassium value in the presence of acidosis is more indicative of total body potassium deficit than is hypokalemia with alkalosis.<sup>7, 8</sup>

The abnormal P waves (figure 1) that were noted in this patient may have reflected hypopotassemia. These abnormal P waves persisted following the correction of hypopotassemia and reduction of venous pressure by the dialysis. Postmortem examination of the lungs did not reveal pulmonary fibrosis or any other reason for cor pulmonale.

In general, the etiology of potassium depletion may be renal or extrarenal. It may occur in chronic nephritis <sup>10</sup> or in primary aldosteronism. <sup>11</sup> Hypopotassemia is not infrequently encountered in the diuretic phase of acute tubular necrosis. The relationship of pyelonephritis to renal wastage of potassium is not clear. Extrarenal potassium depletion may be due to inadequate intake, as in severe anorexia nervosa; <sup>12, 18</sup> and in normal men, negative potassium balance has been induced by reduced intake of potassium. <sup>14</sup> Under such circumstances the gastrointestinal tract becomes an important route of potassium loss. <sup>14</sup>

In diarrheal diseases, potassium depletion, vacuolar nephropathy and even death may occur.<sup>15, 16, 17</sup> Excessive use of laxatives as a cause of potassium depletion and hypokalemic nephropathy in man has been studied thoroughly.<sup>6</sup> Potassium depletion, irrespective of its cause, may result in impairment of function and structure of the kidneys.<sup>4</sup> Defective conservation of potassium secondary to primary renal disease may conceivably cause additional functional and organic impairment of the kidneys.<sup>18</sup>

In acute potassium depletion induced in dogs by dialysis with the artificial kidney, inulin clearance was reduced but could be restored to normal by repletion of potassium. 

In patients with chronic depletion of potassium, renal biopsy and renal function studies indicated that the nephropathy in man is reversible. 

There is, however, experimental evidence that the nephropathy of potassium depletion in rats may become irreversible. 

In our patient, restoration of blood electrolytes within a short period of time did not appear to improve

the renal function. Evidence for this situation in man is deficient.

Acute tubular necrosis, nephritis or primary aldosteronism as a cause of potassium depletion may be ruled out in our patient. The clinical and laboratory data available, however, do not permit diagnostic differentiation among renal tubular acidosis, Fanconi's syndrome and extrarenal wastage of potassium. Renal tubular acidosis is variously known as "renal tubular insufficiency without glomerular insufficiency" 21 or as a renal hyperchloremic acidosis. The basic defect is the failure of acidification of the urine due to decreased ammonia formation, and failure of excretion of titratable acid with increased bicarbonate excretion.22 As a result of this tubular dysfunction, the excessive urinary loss of potassium, sodium and calcium leads to a deficiency of these essential ions and development of osteomalacia. Glomerular function may be impaired, but usually not severely enough to cause azotemia.22 The presenting symptoms and signs are those of osteomalacia, renal calcinosis or nephrolithiasis and potassium depletion. Nephrocalcinosis is a very common feature of renal tubular acidosis and, according to Wrong and Davies,22 was described in 44 of 66 reported cases, and was present in nine of 11 cases reported by them. The diagnosis of this condition is based on demonstration of defective acidification of urine by diminished ability of the kidneys to respond to a load of ammonium chloride.22 The response to an ammonium chloride load is found to be similar in patients with renal tubular acidosis and in those with extrarenal potassium depletion.<sup>22</sup>

Fanconi's syndrome consists of amino-aciduria without amino-acidemia, glycosuria with normal glucose tolerance, hypophosphatemia, hyperphosphaturia and involvement of the skeletal system. A review of 18 adults with this disease up to 1957 revealed that the most prominent and consistent symptom was bone pain.<sup>23</sup> All had elevation of serum alkaline phosphatase, multiple fractures and rarefactions of the bone.<sup>23</sup> Glomerular function may be impaired, and azotemia

may be seen.23

Our patient had some features that are suggestive of primary renal potassium wasting: severe potassium depletion and uremia. But there are no other symptoms or signs usually associated with renal tubular acidosis or Fanconi's syndrome, as discussed above. The history of prolonged use of laxatives and very inadequate dietary intake in this patient suggests the likelihood of prolonged extrarenal potassium wastage. A determination of potassium content in the urine would have furnished an important clue to the question of extrarenal or

renal potassium loss, since urinary potassium content is decreased in extrarenal wastage of potassium,<sup>5</sup> whereas in primary renal loss this is not the case.

Regardless of the etiology of our patient's severe potassium depletion, whether renal or extrarenal, the immediate cause of her death was probably the depletion of potassium and subsequent renal failure. This is in contrast to the usual picture of paralysis with little azotemia.<sup>2, 3, 16, 17</sup> One case reported by Williams and MacMaron <sup>24</sup> showed moderate azotemia. Lesions of the myocardium and striated muscles noted in this patient may also be reflections of profound potassium deficiency.

Since nephropathy of potassium depletion in man has been observed thus far to be a reversible disease, every effort should be made to correct the potassium depletion as well as to treat the renal failure. Metabolic acidosis should be treated vigorously by removal of hydrogen ion, if necessary with the artificial kidney or peritoneal dialysis. In such a complex electrolyte imbalance with renal failure, the artificial kidney, being "an automatic computer," is the unique means of treatment, because of its ability to remove and to add dialyzable substances simultaneously. Hypokalemia can be corrected in this way without inducing the hyperkalemia which might occur by rapid intravenous infusion.

Administration of glucose or a high carbohydrate diet is advocated for the management of acute renal failure. This should be carried out with extreme caution in patients with hykokalemia, since it may further and rapidly decrease the blood potassium concentration. Sudden death during the administration of glucose solution to a patient with hypokalemia has been described.<sup>2, 16</sup>

## SUMMARY

A fatal case of severe hypopotassemia with renal failure is presented. It is suggested that irreversible renal failure may ultimately occur in the nephropathy of potassium depletion in humans. Habitual use of laxatives and inadequate diet over a period of many years are considered to be the causes of potassium depletion in this instance. Degenerative changes in the myocardium and skeletal muscles as well as in the kidneys are described.

#### SUMMARIO IN INTERLINGUA

Un feminina de 52 annos de etate habeva prendite laxativos e clysteres diurnemente e habeva mangiate un inadequatissime dieta durante un periodo de annos. Illa pesava 28 kg. Illa habeva travaliate como cassera usque a quatro dies ante su admission al hospital, quando illa disveloppava crescente grados de dyspnea, orthopnea, e stupor.

Le examine revelava stupor, hypotension, hypercapnea, alte tension venose, digitos hippocratic, e marcate cachexia. Esseva etiam trovate azotemia (con nitrogeno del urea sanguinee amontante a 114 mg per 100 ml), leve grados de anemia, leucocytosis, e marcate disturbation del electrolytos seral. Le kalium seral amontava a 1,8 mEq per litro; le potentia combinatori de CO2 esseva 8,8 mEq per litro; le natrium del sero esseva 127 mEq per litro. Esseva etiam trovate un moderate reduction del chloruro e del calcium del sero e un elevation del phosphoro inorganic del sero amontante a 15,5 mg per 100 ml. Le patiente non se meliorava post le uso de agentes pressori e intravenose solutiones reparatori. Anuria persisteva.

Hemodialyse restaurava le valores del electrolytos del sero a nivellos normal e

reduceva le nitrogeno del urea sanguinee a 40 mg per 100 ml. In despecto de isto le patiente remaneva comatose e moriva le quarte die del sojorno al hospital.

Le necropsia revelava un degeneration vacuolar in le epithelio reno-tubular, de forma characteristic de nephropathia per depletion de kalium. Marcate alterationes degeneratori esseva etiam notate in le musculos skeletic e cardiac.

Il pare que le alterationes tissular de depletion de kalium pote devenir irreversibile. Le perdurative uso de laxativos e clysteres, in combination con le inadequate dieta, esseva apparentemente le mechanismo del depletion de kalium in le presente

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# MASSIVE OSTEOLYSIS OF BONE: REPORT OF A FATAL CASE WITH TEMPORARY RECONSTITUTION OF THE AFFECTED BONE FOLLOWING IRRADIATION \*

By JOHN M. FIORE, M.D., and WILLIAM T. SMYTH, M.D., Albany, N. Y.

The syndrome of acute spontaneous absorption of bone is a rather rare and poorly understood condition. It is often referred to under such descriptive titles as "disappearing bone," "acute spontaneous absorption of bone," "phantom bone" and "idiopathic osteolysis of bone." In the cases reported to date, several common factors seem to occur repeatedly: The patient is usually a young adult in good general health; minor trauma, usually to the affected area, calls attention to the lesion; pain is not a striking symptom; there is no sex predilection. The course of the disease is variable. Cases have been reported where the lesion progresses to a certain size and then remains static. In other instances the lesion may progress to extensive destruction of the affected bone as well as contiguous bony structures. In these latter instances it has usually been found that the lesion was a neoplasm, i.e., lymphangioma, hemangioma, etc. Rarely, the lesion becomes so extensive as either to require radical surgery or to end fatally as a result of secondary involvement of adjoining vital structures.

The etiology of some of these instances of "disappearing bone" is obvious, i.e., hemangioma of bone, lymphangioma of bone, or nonunion of fractures with resorption of varying amounts of the distal fragment. In other cases—and these are the lesions we are concerned with in this report—no common denominator is apparent. All sorts of theories of the etiology have been proposed. Parathyroid tumors have been incriminated, sought for and, so far at least, not found. Loss of local blood supply following fracture seems a reason-

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able explanation in some instances, especially in post-traumatic cases involving the medial end of the clavicle 4 or the carpal bones. A neurotrophic etiology has been suggested in one case with syringomyelia with "spontaneous disappearance" of the left humeral head.<sup>5</sup>

The first case of "disappearing bone" was reported in the Boston Medical and Surgical Journal in 1838.6 An 18 year old male who over a period of two months sustained three successive fractures involving the right humerus experienced a continuous absorption of the humerus over the next 12 years. The patient died at the age of 70 from an unrelated cause. In 1933 a second case was reported in the Journal of Bone and Joint Surgery by Thoma.<sup>7</sup> This was a 36 year old housewife with spontaneous absorption of the mandible and, to a lesser degree, the maxilla, palate and sphenoid bones following dental extraction during the fifth month of her third pregnancy. X-rays of other bones appeared to be normal. Thoma stressed that the bony involvement was that of the distribution of the fifth cranial nerve, and therefore suggested a neurotrophic origin. Subsequent to these reports, sporadic case reports have appeared, so that approximately 30 cases have now been reported in the literature. In seven of 17 cases, adequate follow-up varying from 15 years to as long as 27 years has been possible. In the majority of the cases that were adequately followed, no obvious progression of the disease was noted. However, in one case, reported in 1949, there was a gradual progression of bony resorption over a seven-year period, and at the time of the last report the lesion appeared to be progressing markedly. Several cases were explored surgically to rule out a parathyroid tumor,7,9 and it is noteworthy that in no case was there any definite evidence of parathyroid abnormality. Biopsies of the bone lesion were performed on nine patients. The histologic appearance of the individual lesions varied from that of a lymphangioma 1 or hemangioma 10 to avascular fibrous tissue. Treatment has varied from none at all in some instances, to sympathectomy 2 or bone grafting.11 In most cases, other than bone grafting, the spontaneous absorption of bone progressed in spite of treatment. After review of these cases, one is impressed with the poverty of adequate metabolic studies of these patients. In view of the possibility of local vascular abnormality in at least some of these cases, it is unfortunate that few angiographic and no regional metabolic studies have been reported in any of these patients. 11, 12, 13, 14, 15

The case reported here is that of a young male who remained a definite diagnostic problem until shortly before his death. Repeated attempts at diagnosis were made, including biopsies of the affected area, angiography and extensive general metabolic studies. The early biopsy specimens were reviewed by three eminent pathologists, who concurred that this represented a case of spontaneous absorption of bone. Shortly before death a sarcoma was diagnosed as being present in the area of the bony lesion.

### CASE REPORT

A 26 year old white male, admitted to the hospital on June 18, 1956, stated that he had felt perfectly well until March, 1956, when he experienced sudden onset of piercing pain in the left knee while walking. At first the pain was rather brief and intermittent. During the next three months the pain became more severe and persistent, especially at night. Heat relieved the pain considerably. The patient had

no other complaints. His system review was not abnormal; he had never been seriously ill, and had never had any chronic disease. He did not smoke or drink excessively. He had sustained a sprain of his left knee in 1952. Physical examination revealed that he was in no acute distress. The left leg was slightly shorter than the right, and the right leg was stronger to a moderate degree than the left. His admission temperature, pulse, respirations and blood pressure were well within normal limits. He weighed 135 pounds, and his height was recorded as 5'8". The remainder of the physical examination was entirely within normal limits. The initial impression was that the patient had a possible neurologic disease, but it was soon discovered that his real difficulty was present in the region of the left hip.



Fig. 1. Pelvic film taken approximately two months after initial admission.

Patient ambulatory and complaining of left knee pain.

Roentgenographs of the pelvis showed severe loss of the superior and inferior rami of the left pubis (figure 1). There was also slight deviation of the left side of the bladder toward the midline. The bladder deviation prompted a study of his urinary tract by radiographic and cystoscopic methods. A moderately severe degree of left hydronephrosis and questionable atrophy of the right kidney were found. An open biopsy of the left pubis, which appeared to be absent on the roentgenograms, was performed on June 26, 1956. This tissue was reported as dense fibrous tissue without evidence of bone formation, specific disease or malignant growth. A repeat biopsy, this time from the inferior border of the left ischium, was performed on



Fig. 2. Film three weeks later, following biopsy of ischium.



Fig. 3. Photomicrograph of biopsy of left ischium one month after initial admission. Hematoxylin and eosin, approximately  $120 \times .$  810

July 24, 1956 (figure 2). This tissue was reported as "normal tendon and cancellous bone, containing foci of new bone formation and fibroblastic activity within the marrow." No malignant tissue was seen (figure 3).

Initial laboratory studies on this first admission were as follows: Leukocyte count and differential, within normal limits; hemoglobin, 14.8 gm.; nonprotein nitrogen, 33 mg. per 100 ml.; fasting blood sugar, 98 mg. per 100 ml.; serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen, negative; Bence Jones protein, negative; acid phosphatase, 2 King-Armstrong units; alkaline phosphatase, 5.3 units; total protein, 7.1 gm., with albumin, 5.1 gm., and globulin, 2.0 gm.; ratio, 2.5. Serum calcium was 10.9 and inorganic phosphorus,



Fig. 4. Pelvis seven months after initiation of irradiation, showing "dramatic remineralization of the pelvis."

3.8 mg. per 100 ml. Sulkowitch's test showed more than 27 mg. per 100 ml. of calcium. Because of the evidence of left hydronephrosis, studies were made of urine from each kidney and from the bladder. No abnormalities were found other than a positive culture of a "member of the *Proteus* group" from the bladder urine.

The patient's final admission was on October 18, 1956, for further evaluation and follow-up. Initial studies were of the urinary tract. These revealed bulging of the left side of the bladder toward the midline, moderate trabeculation of the mucosa, and medial displacement of the left ureteral orifice. No bladder biopsy was done. There was a moderate left hydronephrosis, with constriction of the middle third of the left ureter. The right kidney and ureter were normal.

On October 24, 1956, six days after admission, it was decided that irradiation of the left pubic area would be used in an attempt to prevent further osteolysis. There had been no appreciable change in the patient's pelvic bone since his previous

films two months before. It was freely admitted that irradiation was a purely empiric attempt at aiding the patient: no diagnosis had been established, and the patient, while bed-fast and in moderate pain, was not critically ill.

Irradiation was started, using 400 kv. with 4 mm. of copper at 70 cm. target skin distance, utilizing two ports, anterior left pubis (9.0 by 10.0 cm.) and left lateral acetabulum (10.0 by 15.0 cm.). Over a period of 36 days, 2200 r were delivered at a depth of 7.0 cm. through each port. Within six days the patient claimed

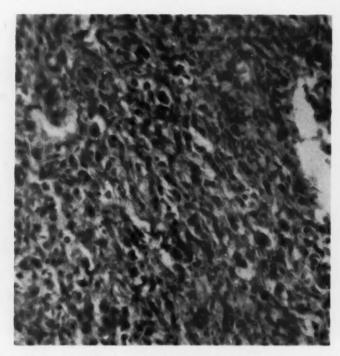


Fig. 5. Photomicrograph of undifferentiated sarcoma from necropsy specimen. Hematoxylin and eosin, approximately  $250 \times$ .

to have a significant decrease in his hip pain and was able to get into a wheelchair. With the decrease in pain, the patient was started on physical therapy and crutch walking. By December 20, 1956, approximately two months after initiation of irradiation, a comparative film showed a significant degree of bone regeneration in the areas of previous loss. By January 28, 1957, there was "dramatic remineralization of the pelvis." During February, March and April, 1957, there was continued improvement in the bony structures, with almost complete regeneration of the left pubic rami, ischium and acetabular regions (figure 4). It was noted, however, that complete closure of the inferior ramus with the pubis did not occur. A particularly striking phenomenon was the regeneration of the bone along the anatomic pathways of a normal pelvis where, five months previously, the films had shown no evidence whatsoever of any bony structure.

During the months of February, March and April, 1957, search was made for

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other skeletal lesions in the chest, skull and extremities, and none was found. Repeat intravenous pyelograms showed definite decrease of the left hydronephrosis, so that by March 14, 1957, the left kidney appeared to be normal, with only slight delay in emptying. During this time also, the patient was receiving physiotherapy, with the hope of eventually allowing weight-bearing on the left leg. This goal was not realized, for the patient had developed flexure contractures of the left knee and hip, and began to complain of increasing pain in the left buttock, posterior and medial thigh, and left knee.

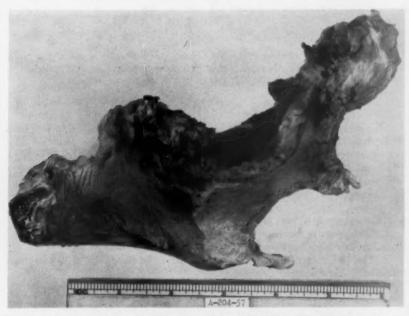


Fig. 6. Necropsy specimen of anterior two thirds of left ilium. Microscopic examination showed no evidence of malignancy within the bone.

During May, 1957, the patient continued physiotherapy, but did not improve. On June 11, 1957, eight months after his second admission and almost one year after his initial admission, a palpable mass was felt in the medial aspect or the upper left thigh. Three days later an aortogram was done, with a report of "abnormal arborization of the vessels in the left internal acetabular area with distortion by a mass in this area." The thigh lesion was biopsied three days later (June 17, 1957), and a very vascular, undifferentiated sarcoma was reported. Twenty-four days after biopsy a fungating mass was protruding through the poorly healing biopsy site. Irradiation of the thigh and groin was begun, and a total tumor dose of 3000 r was given in 26 days to the thigh and groin, using 250 kv., with a half-value layer of 2.5 mm. of copper at 50 cm. target skin distance, utilizing one port, anterior inguinal triangle (15.0 by 15.0 cm.). The lesion regressed considerably, but two draining sinuses resulted, one in the suprapubic area and one in the left groin. Irradiation was completed on August 7, 1957, and on August 10, 1957, the first evidence of pulmonary metastases was seen. Prior to this time the chest had

always been normal on repeated chest roentgenograms. The patient died on September 11, 1957, after a progressive course of weakness and ever-enlarging pulmonary metastases.

At necropsy the findings were those of an undifferentiated sarcoma which had spread to the lungs, retroperitoneal soft tissues of the pelvis, periaortic and left perirenal areas (figure 5). There was extensive necrosis of the neoplasm in the left pubic, ischial and acetabular regions. The bone, which had reconstituted so nicely six months before, was once again absent (figure 6). Only a remnant of ischial tuberosity remained, and most of the anterior border of the acetabulum was absent. It was impossible to determine the site of the primary lesion, due to extensive necrosis and destruction of both the bony and soft tissues of the left pelvic area. Special stains of the neoplasm indicate that it was not a liposarcoma, hemangiosarcoma or osteogenic sarcoma.

From the autopsy findings it is quite certain that the lesion was not a primary tumor of the pelvic bones. It appears most reasonable to believe that the malignancy, whenever it started, arose in the soft tissues of the left pelvic region.

#### COMMENT

Massive osteolysis of bone, or "disappearing bone," is infrequently reported. While most orthopedic surgeons are aware of the lesion, few have actually treated or seen such cases. The number of other clinicians who have seen or treated such cases must be very small. A minimal number of cases has been studied metabolically. At latest reports, probably no more than five or six cases have had truly adequate general metabolic studies. No local metabolic studies have been attempted to date.

The case reported here would seem to indicate several points:

1. "Disappearing bone" is primarily a local phenomenon; general metabolic studies to date have been completely unrewarding.

2. The lesion may occur concomitant with or be the result of a malignant neoplasm in close anatomic proximity.

3. Irradiation may be of some benefit in arresting the process or in restoring the skeletal structure.

While we have no proved answer for the cause of the "disappearing bone" in this case, we do feel that consideration must be given to the theory that in this instance the bone disappeared due to local metabolic competition between a malignant process and the adjacent intact skeleton. It is to be recalled that in the earliest stages of this patient's disease there was evidence of left-sided bladder displacement, hydronephrosis and hydro-ureter. With irradiation, the renal abnormality almost completely disappeared, and at necropsy no evidence of hydronephrosis, hydro-ureter or bladder neoplasm was found. While it is unusual for undifferentiated soft tissue sarcomas, such as fibrosarcomas, neurogenic sarcomas, etc., to respond to irradiation, it is not unheard of. The malignancy in the left pelvic area was almost totally destroyed at the time of autopsy, little remaining in the left pelvis but a gaping defect lined by necrotic slough and portions of the iliac wing and posterior acetabulum. A large amount of neoplasm was present in the lungs and periaortic regions. No evidence of a primary bone tumor was found, nor was there evidence of a bladder neoplasm. One other item is of interest in this case, and that is the fact that, either due to or in spite of irradiation, the pelvic bones regenerated, only to

disappear again before death. Unfortunately, no roentgenographs were taken in the late stages of the disease, and it is not known just when the bone, which had almost completely reformed, once again disintegrated.

It is hoped that future cases of "disappearing bone" can be studied in greater detail in regard to their metabolism, histology, and response to irradiation or other therapy.

## ACKNOWLEDGMENTS

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## SUMMARIO IN INTERLINGUA

Le syndrome de acute e spontanee absorption de osso es un condition rar e mal comprendite. Le patientes es usualmente juvene adultos in bon stato de sanitate, e usualmente un trauma pauco importante tira le attention al presentia del lesion indolor. Iste lesion pote progreder usque a un extense destruction del afficite osso e del adjacente structuras ossee, sed illo etiam pote remaner static.

Varie etiologias es mentionate in le descriptiones de iste casos, incluse hemangioma de osso, lymphangioma, o non-union de fracturas con resorption. Sed in altere casos, nulle denominator commun es apparente.

Le apparentia histologic del lesiones individual variava ab illo de un lymphangioma o hemangioma ad illo de tissu fibrose avascular. Le tractamento ha variate inter nihil del toto e sympathectomia o graffage de osso. In le majoritate del casos, le spontanee absorption progredeva in despecto del tractamento.

Es infelice que pauc studios angiographic e nulle studios metabolic regional se trova includite in le reportos de iste patientes.

Le hic-presentate caso es illo de un juvene masculo qui remaneva un non resolvite problema diagnostic usque a brevemente ante su morte. Le patiente habeva 26 annos de etate. Ille se plangeva de dolores in le genu sinistre, sed le roentgenogrammas del pelve monstrava un sever perdita del ramos superior e inferior del osso pubic sinistre. Specimens bioptic esseva interpretate como indicante un absorption spontanee de osso. Le studios del metabolismo produceva resultatos normal. Le afficite region esseva tractate con 2.200 r accumulate in 36 dies. Un frappante regeneration de osso per vias anatomic esseva effectuate.

Un anno plus tarde, un massa palpabile esseva constatate in le femore sinistre. Le biopsia del massa indicava un non differentiate sarcoma que esseva multo vascular.

Es exprimite le spero que casos futur de "disparition de osso" pote esser studiate plus detaliatemente con respecto a lor metabolismo, lor histologia, e lor responsa a irradiation o altere formas de therapia.

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# CRYPTOCOCCOSIS: A CASE REPORT \*

By Theodore E. Hauser, M.D., F.A.C.P., Carlsbad, New Mexico

CRYPTOCOCCOSIS is a rather uncommon infection which may be either subacute or chronic, and may involve many organs. Almost invariably there is a terminal meningitis.1

Human infections have been found throughout the world; in the United States, they are found chiefly in the southern states. They have also been found in many species of animals, including the dog, cat, horse, cow, guinea pig, monkey and fox. The evidence points to a saprophytic existence of the yeast, independent of human or animal infection. There is no evidence of crossinfection, or of spread from animal to animal or man to man.

Dr. C. W. Emmons isolated the cryptococcus from the soil in 1951, and in further studies isolated it consistently from pigeons' nests. He concluded that pigeons eat contaminated fruits or seeds, and the saprophyte passes through the gastrointestinal tract. He correlates this with several outbreaks of pneumonitis in persons exposed to the droppings when cleaning areas where pigeons have nested.2

The number of cases reported has risen from 43 in 1931 to more than 300

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in 1955,3-4 It is estimated that 50 deaths a year are due to cryptococcic meningitis.

## CASE REPORT

A 56 year old white male attorney became ill on August 27, 1959, complaining of a dull frontal headache, with pain also behind the eyes. Since he had previously had sinusitis, he started taking a tetracycline. Despite this treatment he became progressively worse during the next few days, and was admitted to the hospital August 31, 1959, with severe headache, pain in the back of the neck, fever, and an increase in a nonproductive cough.

This patient had been in good health most of his life except for a chronic, non-productive cough with occasional attacks of sinusitis. During recent months he had become extremely fatigued from overwork. He lived in a country house and kept sheep and chickens on his three acres. He was an ardent hunter of quail and doves, which he frequently hunted over the desert areas.

Physical Examination: The patient was a well developed white male. Height, 76 inches; weight, 210 pounds; temperature, 101° F.; pulse, 80; respirations, 22;

TABLE 1
Results of Spinal Fluid Examinations

Date	Lymphocytes Cu. Mm.	Spinal Pressure	Yeast Cells	Protein Mg./100 Ml.	Sugar Mg./100 Ml.	Chlorides mEq.	Fungus
9-1-59	303	170 mm.		150		132	+
9-4-59	240	170 mm.		95	42	116	+
9-10-59	80	-390  mm.		109	20	116	+
9-11-59	400	500 mm.	Present	89	10		+
9-14-59	173	600 mm.	181/cu. mm.	97	10	100	+
9-17-59	108	500 mm.	42/cu. mm.	131	15	108	+
9-21-59	90		40/cu. mm.	74			+
9-24-59	74	210 mm.	18/cu. mm.	64	50		+
9-26-59	76	-210 mm.	3/cu. mm.				+

blood pressure, 130/70 mm. of Hg. There was tenderness over the right frontal and maxillary sinuses. There was stiffness of the neck, with a positive Kernig's sign. Examination of the heart revealed a normal sinus rhythm. There were no murmurs, and the point of maximal impulse was 1 cm. inside the left midclavicular line in the fifth interspace. The lungs were clear to percussion and auscultation. The liver, spleen and kidneys were not palpable. There were no masses. Rectal examination was negative. Examination of the extremities was also negative. Except for a positive Kernig's sign, the neurologic examination was normal. The initial impression was that the patient had acute sinusitis and, because of the nuchal rigidity, a meningitis, due either to direct extension from the sinuses or to some unrelated cause.

Clinical Course: Initial chest x-ray was negative. X-ray of the sinuses revealed the right maxillary, ethmoid and frontal sinuses to be clouded. Initial complete blood count: hemoglobin, 15.6 gm.; red blood cells, 4,900,000; white blood cells, 12,900, with segmenteds 59, lymphocytes 35, monocytes 3. Urinalysis was negative.

A spinal tap was performed, with an initial pressure of 190 mm. Fluid was clear; Queckenstedt's sign was normal. White blood cell count, 303 per cubic millimeter, with 100% lymphocytes and an occasional "RBC." Protein, 150 mg.%; sugar, 50 mg.%; chlorides, 132 mEq./L. Cultures were taken.

The patient was placed on Panalba for the sinusitis, and a diagnosis of possible lymphocytic choriomeningitis was entertained. During the next four days he ran a low grade fever (99.2° F.), and continued to complain of nausea and frontal headache; there was also some vomiting. On the seventh day of hospitalization diplopia occurred, and his speech became slurred. The spinal fluid showed a decrease in the total cells, protein and sugar content, with the initial pressure increasing (table 1). On the tenth hospital day the patient appeared to be worse, with confusion, bilateral lid drooping, masklike facies, and some increase in the deep tendon reflexes on the left side, with bilateral positive Babinski's.

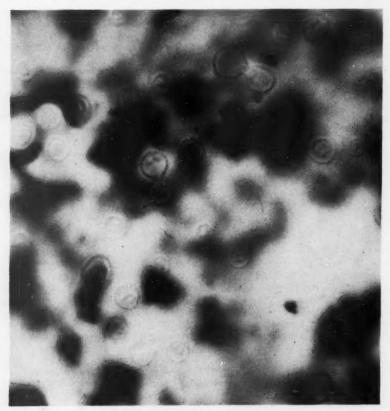


Fig. 1. India ink preparation of spinal fluid, high power, showing yeast cells.

On the following day, because of the patient's progressively downhill course, a neurosurgeon was consulted. A spinal tap was again performed, with removal of cloudy fluid for the first time; under direct smear many yeastlike, spherical cells were seen in an active stage of budding (figure 1). The following morning the initial spinal fluid culture revealed *Cryptococcus neoformans*-like organisms. The patient was then placed on Gantrisin. Amphotericin B therapy was started. The patient had chills and fever following the injection of 60 mg, given over a six-hour period.

The following day his blood urea nitrogen was 61.8 mg.%, but this was attributed to Urevert, given intravenously the previous day in an attempt to lower the spinal fluid pressure.

Following the sixth intravenous injection of amphotericin B, the patient's blood urea nitrogen increased to 45 and 61 mg.%, after which the drug was withheld.

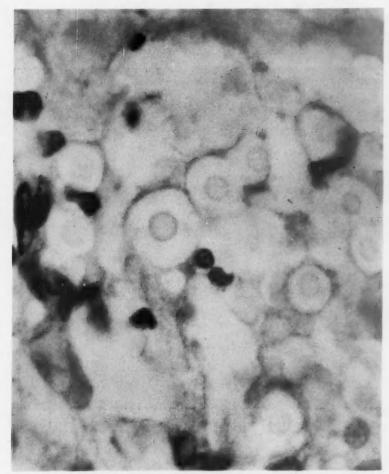


Fig. 2. Brain: showing many cryptorocci, some appearing to be in the budding stage (oil immersion).

Then 0.5 mg, amphotericin B was given intrathecally on September 23 and 26, and intravenously on September 25,

During this entire period the patient appeared to be going downhill, with fluctuations in his blood pressure, a temperature elevation to 101 to 103° F., and convulsions. He developed a severe thrombophlebitis of the left leg, probably sec-

ondary to the administration of parenteral fluids or amphotericin B, or both. Chest x-ray revealed a pneumonitis at the left base. Medrol and penicillin were employed, but the patient died on September 27, the twenty-seventh hospital day.

Miscellaneous Laboratory Studies: Cultures of blood, urine and nasal secretions were negative for fungi. An electrocardiogram showed an incomplete right bundle branch block.

Pathologic Findings: There was evidence of severe meningo-encephalitis, with numerous cryptococci present. There were found in the meninges and brain parenchyma (figure 2), proliferations of fibroblasts with formation of foreign-body-type giant cells.

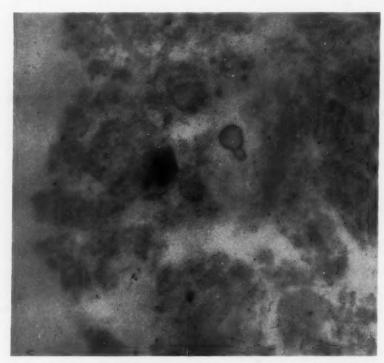


Fig. 3. Budding cryptococcus in the granuloma of the lung (oil immersion).

Lungs: There were hard yellowish nodules, well outlined and irregular, in both upper lobes, varying in size from 0.3 to 1.5 cm. in greatest diameter. No calcification was present. Sections of these revealed central caseous necrosis, surrounded by a fibrous hyaline wall. Occasional cryptococcus organisms were seen within the granulomatous lesions (figure 3).

## COMMENTS

This case was one of pulmonary cryptococcosis of an estimated duration of several years, with a terminal spread to the central nervous system, producing a severe meningo-encephalitis. He presented the clinical findings of a benign lymphocytic choriomeningitis, although on the second spinal fluid tap, with the

finding of a decrease in the lymphocytes and sugar, this diagnosis was discarded. The spinal fluid findings, with a decrease in sugar, are not present in virus meningitis, and suggest an acid-fast bacterium or fungus as the etiologic agent. A more careful examination of the initial spinal fluid with India ink might have revealed the original "RBC's" to be cryptococcus.

The recommended dosage of amphotericin B ranges from 0.5 mg. to 1.5 mg./Kg., given in an infusion of 5% glucose in distilled water over a six-hour period, diluting the drug 1:20.

Toxic effects encountered in this case were chills, fever, vomiting and an increase in headache. The drug also caused an elevation of blood urea nitrogen. A decrease in serum potassium was noted in this case and in one reported by Shields.<sup>5</sup> The cause of the elevation of the blood urea nitrogen is unknown. The elevation usually returns to normal if the drug is temporarily discontinued.

Intrathecal amphotericin was employed when the blood urea nitrogen was elevated and the drug could not be given intravenously. Salicylates, antihistaminics and corticosteroids were employed in an attempt to decrease the toxic reactions, but without results.

Cultures were taken in this patient's house, in the chicken house and in other suspect areas, with negative results. The association of cryptococcus infection with other chronic disease states, including Hodgkin's disease, tuberculosis, sarcoidosis and carcinoma, has long been recognized.<sup>6, 7</sup> The possibility that the granulomatous lesions in the lungs due to cryptococcus have been misdiagnosed must be considered, as the cultures are often negative, and only after careful microscopic examination may one find an occasional cryptococcus.<sup>8</sup>

### SUMMARY

A 56 year old man developed a severe, acute cryptococcic meningo-encephalitis and, despite amphotericin B therapy, died 27 days after the onset of his illness. In addition to the severe meningo-encephalitis, autopsy revealed cryptococcus granulomas in the upper lobes of both lungs.

## ACKNOWLEDGMENT

The author wishes to express his gratitude to Dr. Leroy Miller, neurosurgeon, of Albuquerque, New Mexico, for his assistance in the management of this case; and to Dr. Fred Haynes, pathologist, of Carlsbad, New Mexico, who performed the autopsy.

## SUMMARIO IN INTERLINGUA

Cryptococcosis—causate per un organismo saccharomycetoide, Cryptococcus neoformans—es un infection incommun que pote esser subacute o chronic e que pote afficer multe differente organos. Terminalmente meningitis es presente quasi sin exception. Le condition es distribuite extensemente. Intra le Statos Unite illo es plus commun in le statos del sud.

Un masculo de 56 annos de etate habeva experientiate le declaration recente de obtuse cephalalgias frontal con dolores retro-orbital e basse grados de febre. Tres dies subsequentemente ille esseva hospitalisate a causa del disveloppamento de rigiditate del collo. Le examine roentgenographic demonstrava sinusitis. Un puncturation spinal revelava le presentia de 303 lymphocytos per millimetro cubic e erythrocytos sporadic. Le diagnose original de acute choriomeningitis lymphocytic esseva abandonate quando un subsequente puncturation spinal revelava un reduction del sucro in le liquido spinal. Le decime die del hospitalisation, le cultura de liquido spinal

pro fungos revelava le presentia de cryptococcos. Amphotericina B esseva prescribite, sed le patiente continuava deteriorar se, con vomito, algor, febre, e coma. Ille moriva un mense post le declaration del morbo.

Le constatationes pathologic includeva multiple micre granulomas pulmonar e grave meningo-encephalitis. Es opinate que terminalmente il occurreva un propaga-

tion ab le lesiones pulmonar verso le meninges.

Le dosage de amphotericina B variava inter 0,5 e 1,5 mg per kg de peso corporee. Le administration esseva per via intravenose a intervallos de sex horas. Le effectos toxic notate esseva algor, febre, vomito, e un exacerbation del cephalalgia. Le droga etiam causava un elevation del nitrogeno de urea sanguinee. Le causa de iste augmento non es cognoscite. Es mentionate le association de infection cryptococcic con altere morbos chronic como morbo de Hodgkin, tuberculose, sarcoidosis, e carcinoma. Le difficultate del diagnose de lesiones granulomatose in le pulmon que es causate per cryptococcos es discutite. Le culturas ab le lesiones pulmonar es frequentemente negative, e il es alora solmente post le plus meticulose examine microscopic de specimens histologic que on trova un cryptococco occasional.

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## TRANSIENT HEMIBALLISM \*

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Hemiballism is a hyperkinesia,¹ consisting of bizarre involuntary movements, which occurs when the subthalamic nucleus of Luys or its pathways are damaged or destroyed.²-6 It has been shown in animal experiments that this lima bean-sized nucleus must be at least 20% destroyed for symptoms to be manifested clinically, and that a correlation exists between the severity of

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symptoms and the percentage of destruction.<sup>7</sup> The nucleus appears to regulate cerebral coördination.<sup>5</sup> Its destruction removes the regulating mechanism, and the resulting hemiballism is due to other surviving structures,<sup>8</sup> since animal experiments prove that the involuntary movements are not produced by stimulation of the nucleus or its pathways.<sup>9</sup>

The lesion is usually contralateral, 2, 10 but rare cases of homolateral involvement have been observed. The latter is apparently due to (Forel's) decussation of nerve fibers. The homolateral pyramidal tract must be intact for the movements to occur. 1, 4, 11

The remarkable hyperkinetic involuntary movements are present at rest as well as with voluntary motion.<sup>6,11</sup> They disappear during sleep, and thereby resemble chorea.<sup>2,6</sup> For this reason, hemiballism has been called "apoplectic hemichorea." <sup>1,3,4</sup> The movements are constant and rapid, and have no regular rhythm.<sup>11</sup> The limbs are thrown and flung about.<sup>2,6</sup> The hyperkinesia may resemble a baseball pitcher's wind-up,<sup>12</sup> and the patient may attempt to fix the affected limb or limbs with the uninvolved side. In hemiballism the axial and proximal muscles of the extremities are affected.<sup>2,6</sup> This contrasts with athetosis, in which the distal muscles have vermiform involuntary motion.<sup>11</sup>

The etiology of the lesion of hemiballism is usually vascular, and the posterior cerebral artery and its branches are frequently involved.<sup>1, 4, 8, 13, 14</sup> Patients developing the syndrome usually have generalized arteriosclerosis or hypertension, and often a combination of both.<sup>1, 2, 15</sup> They have been reported to have a mean age of 68 years.<sup>1, 2, 6, 13, 15</sup> An increased incidence of diabetes mellitus is seen.<sup>6</sup> Hemiballism has resulted from metastatic malignancies,<sup>6, 14, 16</sup> tuberculomas, gummas, trauma, multiple sclerosis and brain abscesses.<sup>6, 11</sup>

Onset of signs is most often abrupt 4, 6, 14, 15 and progressive.<sup>2, 4</sup> The left side of the body is more often involved.<sup>10, 12, 18, 15</sup> Monoballism is uncommon but has been seen.<sup>2, 6</sup> In 55% of cases the upper extremity is more incapacitated. About two thirds of patients have facial involvement <sup>10</sup> and, if this occurs, speech, swallowing and respiration are usually disturbed.<sup>4</sup> Autonomic dysfunction may also accompany hemiballism, and may appear in the form of hyperhidrosis, vasodilatation, abnormal salivation, lacrimation, exophthalmos and oculopupillary symptoms.<sup>2, 14</sup> Mental changes are not associated, but may exist prior to onset of the hyperkinesia.<sup>2</sup> Hyporeflexia has been noted on the affected side.<sup>8,11</sup>

Until recently the prognosis of hemiballism has been thought to be extremely grave, with death occurring in a few weeks.<sup>2, 4, 18, 15</sup> The causes of death are usually exhaustion and pneumonia.<sup>1,4,8</sup> The patients may resort to suicide. However, in direct contrast to the previously accepted belief that the syndrome was invariably fatal, a recent review of the prognosis of hemiballism indicates gradual recovery in 12 of 14 patients.<sup>6</sup> Therapy has been varied but now offers more promise. Various neurosurgical procedures have been performed, with some success.<sup>11, 17, 18</sup> Now that spontaneous recovery has been observed, it is recommended that neurosurgery be delayed until it is obvious that spontaneous improvement will not occur or until dictated by clinical deterioration. Chlorpromazine and promazine therapy has been associated with improvement in several cases, and this may be due to drug depression of abnormal impulses originating in the extrapyramidal system which appear when the inhibition of the nucleus of Luys is removed.<sup>6, 10</sup>

The following case of hemiballism is presented because of the circumstances which preceded the clinical syndrome and the ultimate recovery which followed. A possible mechanism in the etiology of this case and its implications are discussed.

### CASE REPORT

A 70 year old white male was admitted on December 30, 1957, to the Veterans Administration Hospital complaining of severe chest pain. His past history revealed documented hypertension of 18 years' duration, treated syphilis, moderate chronic alcoholism, and a posterior myocardial infarction which had occurred two years before admission.

The patient stated that he had noted severe chest pain on the day of admission. Dyspnea but no diaphoresis had accompanied the pain. He appeared to be moderately confused, and his sister stated that this confusion had been present for several months, Significant physical findings were: blood pressure 210/110 mm. of Hg (supine), increased anteroposterior chest diameter, scars of chorioretinitis in the right fundus and marked arteriolar narrowing. No abnormalities of the heart were noted. Nontender, firm hepatomegaly extended 3 cm. below the right costal region. No clubbing, edema, abnormal movements or cyanosis of the extremities was observed.

Laboratory: Serial electrocardiograms were interpreted as showing left ventricular hypertrophy and an old posterior myocardial infarction. No acute changes were seen. Two serologic tests for syphilis were negative. Serial determinations of the sedimentation rate, C-reactive protein, white blood cell and differential counts were normal. Urine specimens contained an occasional white blood cell and a few hyaline casts. Liver function tests were within normal limits. Lumbar puncture was not performed.

Hospital Course: The patient was observed for a possible acute myocardial infarction. The subsequent course was not compatible with this diagnosis.

On December 31, 1957, one day after admission, oral treatment with hydralazine, 10 mg. three times a day, and phenobarbital, 30 mg. four times a day, was begun (figure 1). The drugs were discontinued 36 hours later because of increasing confusion of the patient and inability to keep him at bed-rest. On January 2, 1958, his blood pressure fell to 168/92 mm. of Hg (figure 1). Orthostatic hypotension did not occur.

A day later marked left hemiballistic movements were first noted. The arm motions were more pronounced than those of the leg. The patient's gait was unsteady, due to the violent, involuntary movements. He was able to control the flailing left hand by holding it with the right hand or by sitting on it. The hyperkinesia was absent during sleep. The patient appeared to be oblivious of this remarkable change and did not complain. His mental confusion was unchanged.

The patient was given 25 mg. of intramuscular prochlorperazine on January 4, 1958. The following day the oral preparation was substituted in doses of 10 mg. four times a day, and reduced to three doses daily on January 8, 1958, with similar clinical effects. The hemiballistic movements gradually diminished in intensity, and completely disappeared by January 8, 1958, four days after they had appeared. They did not recur. Prochlorperazine was discontinued on January 13, 1958, after a total of nine days. Despite the disappearance of the hyperkinesia, mental confusion persisted and the patient became a management problem on the cardiology ward. A psychiatric consultant thought that he had a chronic brain syndrome which was associated with cerebral arteriosclerosis, hypertension and alcoholism, and the patient was therefore transferred to the psychiatric hospital.

Six months after the transient episode of hemiballism, serial blood pressure

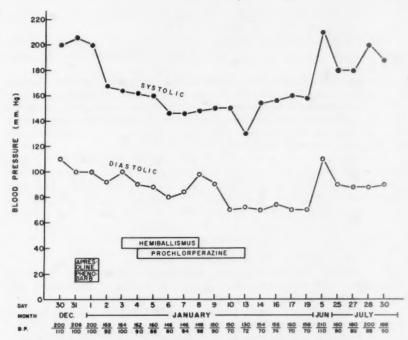


Fig. 1. Temporal relationships between the administration of drug therapy, the period of hemiballismus and the serial blood pressure determinations recorded during hospitalization of the patient.

determinations revealed that the patient was again hypertensive, with systolic pressures ranging from 180 to 210 mm. of Hg (figure 1). No abnormal involuntary movements had been noted since January 8, 1958, during prochlorperazine therapy. The only abnormality observed during a complete neurologic examination on June 5, 1958, was a dissociation of arm and leg movements while walking. At that time the patient's blood pressure was 210/110 mm. of Hg. His organic brain syndrome was unchanged, and for this reason he was still hospitalized as a custodial patient.

## DISCUSSION

The etiology of this temporary episode of hemiballism is not clear. A suggested mechanism is that lowered cardiac output resulted in cerebral anoxia in this elderly, arteriosclerotic male with known hypertension. The cerebral anoxia temporarily affected the right nucleus of Luys, or its pathways, and produced the remarkable hyperkinetic activity observed.

The decreased cardiac output may have been due to either coronary artery insufficiency or acute relative hypotension, caused by antihypertensive drugs and semi-bed-rest. It is known that acute hypotension, particularly in patients with cerebral arteriosclerosis and atherosclerosis, may be a significant factor in the pathogenesis of cerebral vascular accidents.<sup>20</sup> Experiments with both

hydralazine and barbiturates, which the patient received on admission, have shown no significant change in cerebral blood flow.

The systolic blood pressure spontaneously returned to its former hypertensive levels (180 to 210 mm. of Hg) and remained. No further attempts were made to lower it.

The hemiballistic movements ceased during the prochlorperazine therapy. It is impossible to be certain whether the drug suppressed the dyskinesia or whether spontaneous recovery occurred while it was being given, since the abnormal movements stopped during the treatment period and did not recur after the drug was discontinued. However, the dyskinesia was maximal when prochlorperazine therapy was instituted.

The unusual course noted in this case suggests an additional potential hazard in the therapy of elderly hypertensive patients which previously has not been publicized. Spontaneous recovery can occur in hemiballism, and drug therapy may be helpful in some cases. Neurosurgery may be utilized if the former fail, or a downhill course ensues.

## SUMMARY

- 1. A case of transient left hemiballism is reported.
- 2. A possible etiology is an acute systolic hypotension due to diminished activity and antihypertensive drug therapy or coronary insufficiency, with resultant cerebral anoxia.
- 3. Eventual recovery of this patient and others recently reported suggests more favorable prognosis of this dyskinesia.
- 4. A hazard of antihypertensive drug therapy is stressed in older, arterio-sclerotic patients.

#### SUMMARIO IN INTERLINGUA

Es discutite le pathogenese, le syndrome clinic, le therapia, e le prognose de hemiballismo. Un caso es presentate. Le patiente esseva un masculo de racia caucasian de 70 annos de etate con antecedentes de hypertension, infarcimento myocardial, lues tractate, e alcoholismo chronic de forma moderate. Un transiente episodio de hemiballismo occurreva post un attacco de insufficientia coronari e hypotension relative. Le declino del tension de sanguine esseva le effecto del medication o del allectamento o de un reduction del rendimento cardiac.

Le resultante hemiballismo se initiava dramaticamente e esseva tractate con prochlorperazina. Post quatro dies de dyscinesia le movimentos involuntari dispareva. Cinque dies plus tarde le droga esseva suspendite, e le hemiballismo non repareva. Cinque menses plus tarde le patiente esseva hypertensive (210/110 mm de Hg), sed hemiballismo non habeva recurrite.

Un graphico delinea le relationes temporal inter le administration del droga, le periodo de hemiballismo, e le alterationes in le tension del sanguine. Le possibile etiologia in iste caso es discutite. Es sublineate le hasardo potential de therapia hypotensive in subjectos de etate avantiate. Le probabilitate de un prognose favorabile in iste typo de dyscinesia es signalate. Iste facto non esseva adequatemente recognoscite ante le articulo que Hyland e Forman publicava con respecto a iste thema in 1957.

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#### BILATERAL MYXOMAS OF THE HEART\*

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Unilateral atrial myxomas have been reported with increasing frequency in the past few years. 1, 2, 3 The left atrium is involved more commonly than the right, the ratio being about three to one. The present case of large peduncu-

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lated myxomas occupying both the right and left atria is believed to be the first such case reported.

## CASE REPORT

A 22 year old white female student entered Seaside Memorial Hospital on August 20, 1957, complaining of cough and fatigue. She had been well until May, 1957, when fever, generalized aches and weakness were present for a few days. A rapid heart and a murmur were said to have been heard at that time. She again

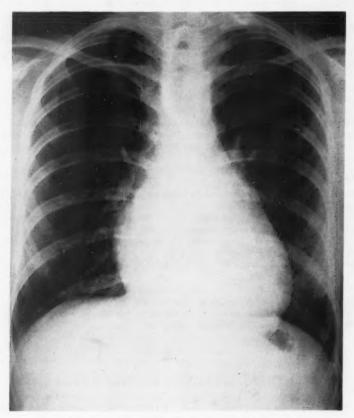


Fig. 1. Posteroanterior roentgenogram of thorax.

felt well until July 2, 1957, when, on vacation in Mexico, she developed a nonproductive cough, exertional dyspnea, watery diarrhea and somnolence. A few days later severe chest pain caused her to be hospitalized in Mexico City, where a cardiologist informed her she had a heart condition and pleurisy. Feeling better, she resumed traveling despite fatigue, cough, anorexia and intermittent diarrhea. On returning home July 28, she first noted abdominal distention. In addition, she noticed excessive perspiration, heat intolerance, palpitation and generalized joint aches without redness or swelling.

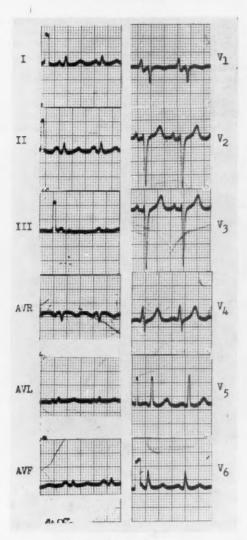


Fig. 2. Electrocardiogram.

The past history was not remarkable except for mild hay fever and penicillin sensitivity. On examination two years previously no murmur had been heard,

Examination revealed a well developed, fairly well nourished, pale girl in no distress. Oral temperature was 98° F.; pulse, 120; respiration, 20; blood pressure, 100/60 mm. of Hg. There were many dark brown to black freckles on the skin. The fundi were normal; the pharynx was clear; no petechiae were seen. Vigorous venous pulsations were seen in the neck. The heart was rapid and regular. At

the apex, located in the fifth interspace at the midclavicular line, a loud harsh murmur filled systole. Superimposed was a short, high-pitched squeak. In the second left interspace a continuous blowing murmur was heard, louder in systole. In the left third and fourth interspaces a diastolic murmur was accentuated in the left lateral position. The chest was clear. There was minimal cyanosis. A nontender liver was felt 2 cm. below the right costal margin. There was no edema, clubbing or splinter hemorrhages. The spleen was not felt.

The laboratory findings were as follows: white blood cells, 10,200, with 3 stab forms, 64 polys, 29 lymphocytes, 3 monocytes and 1 eosinophil; hemoglobin, 14.3 gm.; red blood cells, 4 million. Catheterized urine: occasional white blood cell;



Fig. 3. Atria viewed from above. One of the small myxomas of the right atrium is also seen.

culture, sterile. Throat culture: Neisseria catarrhalis and alpha hemolytic streptococcus; negative for Corynebacterium diphtheriae. Blood culture, sterile after two weeks. Antistreptolysin titer, 125 Todd units and 100 Todd units on two occasions; L.E. cell test, negative; Kahn and serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen, nonreactive; second strength PPD and coccidioidin skin tests, negative.

The chest x-ray film disclosed a localized convexity in the region of the left atrium, compatible with mitral valvular disease (figure 1). The lung fields were clear. Electrocardiogram showed low voltage in the standard leads, prominent diphasic P waves in  $V_1$ , and notched P waves in  $V_4$  and  $V_5$ . PR and QT intervals were within normal limits (figure 2).

A tentative diagnosis of rheumatic carditis was made and intravenous ACTH was started. The oral temperature was elevated to 100° F. during the first 10 days, but thereafter remained below 97° F. The pulse slowed and the continuous murmur at the base of the heart disappeared. On August 29, 1957, the patient was discharged on bed-rest, aspirin, prednisolone, Gantrisin, Diamox, and a low salt diet.

On September 10, 1957, she was re-admitted because of dyspnea, cyanosis and anorexia. The oral temperature was 96° F.; pulse, 124; respiration, 32; blood pressure, 90/85 mm. of Hg. Jugular venous pulsations were again prominent. The heart sounds at the apex were as before. The rhythm was regular. A diastolic gallop was present along the left sternal border; here also a to-and-fro crunching

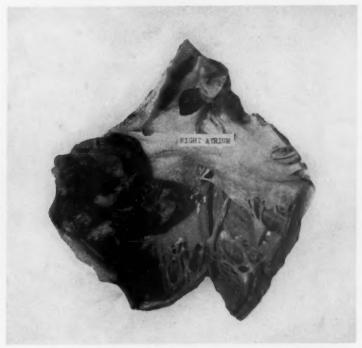


Fig. 4. Right atrial myxomas viewed from the lateral portion, showing protrusion of the largest through the tricuspid orifice.

rub was now heard.  $M_1$  and  $P_2$  were accentuated. Pulsus paradoxus was present. A tender liver extended 5 cm. below the right costal margin. There was pitting edema to the midpoint of the lower legs.

Laboratory findings on second admission: white blood cells, 13,800, with normal differential; red blood cells, 4.8 million; hemoglobin, 14.3 gm.; sedimentation rate (Wintrobe), 20 mm. in one hour. Catheterized urine showed 2 to 3 red blood cells and 1 to 12 white blood cells per high power field. C-reactive protein, 4 plus; L.E. cell test, negative; protein-bound iodine, 4.4 µg.; albumin-globulin ratio, 3.6/2.0 gm.; thymol turbidity, 1.6 Shank units; gastric washings, negative for acid-fast bacilli on smear and culture.

Fluoroscopic examination revealed moderate diminution of pulsations around the entire cardiac silhouette. The barium-filled esophagus was displaced posteriorly. A suggestion of a double shadow was seen through the heart in the left atrial area.

Following strict bed-rest, salt restriction, diuretics, oxygen and digitalis there was general improvement. The patient was discharged on October 4, 1957.

The patient was re-admitted on November 4, 1957, when she appeared emaciated and critically ill. She was confused and semistuporous. Marked cyanosis of the cheeks and fingernails was present. Temperature was 94° F.; pulse, 120; respiration,

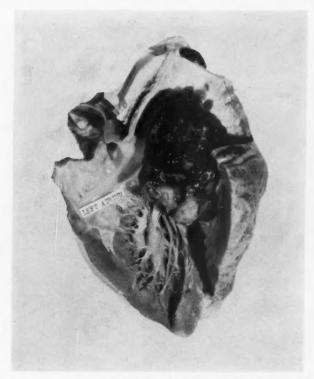


Fig. 5. Left atrial myxoma viewed from the lateral portion, showing protrusion through the mitral orifice.

28. The heart sounds were unchanged. A few moist râles were heard at both bases. Deeply pitting edema was present in both legs, extending to the sacrum. The knees were swollen, hot and tender. The hepatic edge was at the level of the iliac crest. Venous pressure was 240 mm. water. Circulation times: Decholin, 37 seconds; ether, 13 seconds. Hemoglobin was 14.6 gm. The albumin-globulin ratio was 1.2/3.7 gm.; blood urea nitrogen, 42 mg. Serum sodium was 129 mEq./L.; potassium, 5.7. Antistreptolysin titer was 50 Todd units. The chest x-ray film showed infiltration in both lung fields, particularly in the lower lobes, but no change in cardiac size or configuration. The electrocardiogram appeared as before.

Cyanosis and dyspnea became profound. The blood pressure became unobtainable, and the patient died 30 hours after admission.

Autopsy: The heart weighed 480 gm. The right atrium (figures 3 and 4) contained a pedunculated, polypoid, hemorrhagic, glistening, soft, reddish tan tumor measuring 85 by 65 by 55 mm. The pedicle was attached to the lateral atrial wall

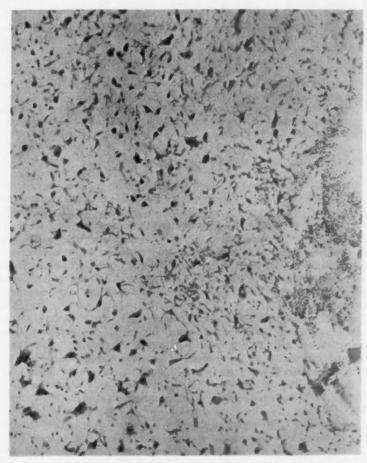


Fig. 6. Photomicrograph of myxoma, showing stellate cells in loose fibrillar myxomatous connective tissue. Areas of hemorrhage are present.  $(\times\,120)$ 

3 cm, from the orifice of the coronary sinus. The tumor protruded partially through the orifice of the tricuspid valve. Three smaller, nonpedunculated tumors were also present in the right atrium. They measured 20 by 15 by 10 mm., 5 by 5 by 3 mm., and 5 by 5 by 3 mm., respectively.

The left atrium (figures 3 and 5) also contained a pedunculated, polypoid hemorrhagic tumor which measured 75 by 55 by 40 mm. The pedicle was attached near

the fossa ovalis. The mass protruded partially through the orifice of the mitral valve. The right ventricle and right and left atria were dilated. The leaflets of the mitral and tricuspid valves were normal, and there was no dilatation of the valvular rings. The epicardium displayed multiple petechial hemorrhages. No pericarditis was evident. The coronary vessels were patent and normal in appearance.

The lungs weighed 800 gm. each and, on section, revealed multiple recent hemorrhagic infarctions, varying from 2 to 15 cm. in diameter. The medium and small pulmonary arteries contained multiple emboli. The liver weighed 1,800 gm. and exhibited typical passive congestive changes. Stellate scars were present in the cortex of both kidneys. No recent or old infarcts were noted in the liver, spleen or adrenal glands.

Histologically, the tumors were composed of stellate cells embedded in a myxomatous connective tissue. Some multinucleated tumor cells were present. There was no evidence of malignancy (figure 6). The infarcts in the lungs were all recent. The pulmonary artery emboli were composed of organized blood elements. No tumor cells were present in the emboli.

## DISCUSSION

Simultaneous growth of benign tumors in each atrium has not been reported previously. The absence of a common site of pedicle attachment to the atrial septum as well as the presence of other smaller myxomas in the atria implies a multifocal origin of the tumors, probably from multiple embryonal rests.

The clinical course amply justified the diagnosis of acute rheumatic pancarditis. There were intermittent fever, tender swollen joints, a friction rub, congestive failure, gallop rhythm, a loud systolic murmur, a transient diastolic murmur, and a short, high-pitched systolic squeak. Laboratory findings of a slightly elevated antistreptolysin titer and a 4 plus C-reactive protein tended to affirm this impression.

Cardiac tamponade was mistakenly diagnosed at one time because of the prominent pulsations of the cervical veins, friction rub, small pulse pressure, pulsus paradoxus, and the low amplitude of the QRS complexes. Thus the case, despite the bilaterality of the tumors, is another classic illustration of the capacity of myxoma to masquerade as other cardiac diseases. Indeed, because of its rarity and lack of a constant pathognomonic sign, it was not until 1951 that the first antemortem diagnosis of atrial myxoma was made.<sup>4</sup>

An uncommon disease can be suspected by knowing the common diseases which it simulates.<sup>5</sup> In myxoma, this is frequently rheumatic mitral valvular disease, because 75% of myxomas arise in the left atrium and impinge upon the mitral valve to produce the typical murmur, radiographic appearance and electrocardiographic features of mitral stenosis.<sup>6</sup>, <sup>7</sup>, <sup>8</sup>, <sup>9</sup>, <sup>10</sup>, <sup>11</sup> Should the tumor wedge in a commissure of the valve, mitral regurgitation may result.

With the triad of murmur, fever and emboli, subacute bacterial endocarditis is simulated next in frequency. Of 20 recent consecutive case reports of myxoma collected by Gleason, 13 simulated mitral stenosis and five, subacute bacterial endocarditis.<sup>3</sup> In isolated instances of unique placement, pedicle length or emboli, other diseases are imitated. Stokes-Adams attacks may occur, especially with certain postural changes.<sup>2</sup> Lekisch reported a case with predominant pulmonary insufficiency that was suspected to be miliary malignancy or the Hamman-

Rich syndrome on the basis of the fine pulmonary infiltrations.<sup>12</sup> This eventually proved to be pulmonary hemosiderosis secondary to a left atrial myxoma. A case recently reported by Kroopf and Peterson presented as coronary thrombosis and congestive failure.<sup>13</sup> Brewer described a myxoma which hung free in the left ventricle on a long pedicle attached to the atrial septum.<sup>14</sup> When this patient bent forward, the aortic valve was obstructed. Tumor fragments which act as emboli have accounted for some bizarre presenting symptoms, among them anuria (aortic embolism blocking the renal arteries),<sup>15</sup> paralysis of the legs with back pain (saddle embolus at the aortic bifurcation),<sup>16</sup> and hemiplegia (middle cerebral artery embolism).<sup>17</sup>

Myxomas of the right atrium obstruct cardiac inflow and present the syndrome of right heart failure.<sup>18, 19</sup> If thrombi or tumor fragments break off, pulmonary embolism occurs.<sup>20</sup> Should relative tricuspid stenosis be severe, a right-to-left shunt may result through an interatrial septal defect.<sup>21</sup>

Regardless of which atrium is involved, the clinical course is a progressive downhill one, ending in death usually within a year after the onset of symptoms. Sudden death is frequent, and in such instances the tumor may be wedged in the mitral ring. Conversely, one patient apparently harbored a myxoma for 43 years before succumbing to another disease.<sup>22</sup>

Valuable clues to aid in the diagnosis of myxoma can be found elsewhere.2, 8, 23, 24 Most authors stress the characteristic change in murmur or symptoms produced by a change in the patient's position. We wish to mention certain clinical features exhibited by our case which have not been sufficiently emphasized previously. First, there was extreme weakness, with anorexia, hypotension, hypothermia and lassitude, characteristic of adrenal insufficiency or starvation. This clinical picture was not unique, as perusal of other reports reveals low temperature and small pulse pressure as frequent occurrences.2, 13, 19, 24 Progressive pigmentation of the skin has been noted.20 A patient with left atrial myxoma recently observed in this institution had depressed steroid excretion and hyponatremia.25 This cachectic state may be present with either right or left atrial myxoma, and is due to the reduction of cardiac output caused by either the obstructed valve or the restriction of free blood flow through the atrium by the space-occupying tumor. Neurologic signs and angina, when not due to emboli, are further complications of low cardiac output. In extreme cases, gangrene of the tips of the fingers, toes or nose results.<sup>20</sup>

Second, and perhaps as a result of cardiac cachexia, is the electrocardiographic sign of low voltage of the QRS complexes, also observed by others.<sup>6, 12, 19</sup>

Third, the P waves were broad and tall in Lead II and sharply biphasic of the plus-minus type in  $VR_3$  and  $V_1$ , indicative of right atrial enlargement. Such "P pulmonale" configuration as a single finding without axis deviation is rare, and should focus attention on disease of the atrium or an elevated pulmonary arterial pressure.

Fourth, the rub heard in this case was scratchy, localized over the sternum, and present in both systole and diastole. Since no evidence of pericarditis was observed post mortem, the rub was apparently produced by the motion of the myxoma(s) against the endocardium. A rub was also heard in one of the cases reported by Ellis et al.<sup>19</sup> Myxoma must be added to a small list of conditions other than pericarditis (aortic valvular disease, bulging pulmonic artery) which might produce friction rubs.

Fifth, a high-pitched musical systolic squeak at the apex is presumably produced by the vibration of a structure in or around the mitral valve at its natural resonant frequency. The resulting musical tone (single sine wave oscillation) is in contrast to the noise (many different oscillations) characterizing most other murmurs. We have heard such sounds occasionally in elderly patients with calcified mitral valves, and occasionally during the course of active rheumatic carditis. It was a constant finding in our case, although it also has been heard transiently in other cases of myxoma. (a) 25 Obviously it cannot be considered pathognomonic of a tumor, but its presence should suggest the possibility.

The diagnosis of myxoma is still made predominantly at autopsy. Occasionally one is found at surgery when a stenotic valvular lesion is anticipated. Angiocardiography remains the best means of diagnosing myxoma. Antemortem diagnosis will be improved only if the possibility is entertained in any cardiac disease exhibiting a relentless downhill course without unequivocal evi-

dence of other cardiac lesions.

Successful surgical removal has been reported in 10 cases, six with the use of extracorporeal circulation, and four with hypothermia.<sup>10, 21</sup>

#### SUMMARY

The first reported case of large pedunculated myxomas occupying each atrium is presented. The course, similar to the usual course of unilateral myxoma, was that of persistent cardiac failure unresponsive to therapy. Active rheumatic fever and cardiac tamponade were simulated.

Clinical signs discussed which may be helpful in suspecting atrial myxoma are cachexia, low voltage QRS complexes, "P pulmonale" waves, a friction rub,

and a high-pitched systolic squeak.

It is important to be aware that this rare malady usually masquerades as a common heart disease, since successful operative removal is now possible.

## SUMMARIO IN INTERLINGUA

Un femina de 22 annos de etate se plangeva de debilitate, tusse, dyspnea, somnolentia, arthralgia, e palpitation. Le cardio-auscultation demonstrava un prolongate, aspere murmure systolic apical con un stridor superimponite. In le secunde interspatio sinistre, un murmure systolic e diastolic esseva constatate. Plus tarde, un persistente ruito de friction sternal esseva presente. Altere constatationes esseva pulsation vigorose del venas jugular, basse tension de pulso, pulso paradoxe, allargamento del hepate, e edema. Le electrocardiogramma monstrava un basse voltage in le derivationes standard e prominente undas P diphasic in V1 e indentate undas P in V4 e V5. Le apparentia radiographic esseva simile a illo de stenosis mitral. Le diagnoses clinic esseva pancarditis rheumatic e tamponage pericardial. Le patiente moriva sex menses post le declaration del morbo.

Al necropsia le corde pesava 480 g. Le atrio dextere contineva un polypoide tumor de color rubio-brun, mesurante 85 per 65 per 55 mm, con un pediculo attachate al pariete atrial lateral. Le atrio sinistre contineva un simile tumor, mesurante 75 per 55 per 40 mm, con un pediculo attachate vicin al fossa oval. Le tumores protrudeva partialmente per le correspondente valvulas atrioventricular. Le atrio dextere extiam contineva tres micre tumores sin pediculo. Le valvulas exhibiva núlle anormalitate. Le pulmones monstrava multiple infarcimentos recente secundari a embolos in le arterias pulmonar de dimension intermediari e micre. Nulle embolos

tumeric esseva trovate. Histologicamente le tumores esseva componite de cellulas stellate e de rar multinucleate cellulas includite in myxomatose tissu conjunctive. Nulle malignitate esseva evidente. Apparentemente le tumores habeva lor origine in multiple restos embryonal.

Iste caso, in despecto del bilateralitate del tumores, es un bon exemplo pro illustrar le capacitate de myxoma de simular altere morbos cardiac. Le morbos imitate le plus frequentemente es stenosis mitral e subacute endocarditis bacterial.

Certe aspectos clinic del presente caso merita esser mentionate como indicios diagnostic. Primo, cachexia esseva presente in consequentia del reducite rendimento cardiac. Secundo, le basse voltage del electrocardiogramma esseva forsan un resultato del stato cachectic. Tertio, un configuration de "P pulmonal" esseva presente sin deviation de axe e ergo dirigente le attention verso le probabilitate de un morbo atrial. Quarto, un presistente ruito de friction esseva presente, apparentemente producite per le motion del myxoma(s) contra le endocardio. Quinto, un stridor altisonante systolic apical esseva audibile, simile a illo que es notate occasionalmente in calcification del valvula mitral o de active febre rheumatic.

Angiocardiographia es le melior methodo pro le diagnose de myxoma. Usque al presente, ablation chirurgic ha succedite in 10 casos. Le possibilitate de myxoma deberea esser prendite in consideration in omne caso de morbo cardiac exhibiente un irrelentante deterioration sin evidentia inequivoc de altere lesiones cardiac.

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## PRIMARY CHONDROSARCOMA OF THE LUNG\*

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PRIMARY chondrosarcoma of the lung is a rarely described pulmonary disease. Following is a history and brief summary and discussion of a case found at Temple University Hospital. The case is known to be of 11 years' duration.

#### CASE REPORT

A 53 year old divorced Negro female domestic worker entered Temple University Hospital for the second time on May 1, 1958, with the chief complaint of chronic fatigue and because of an abnormal chest x-ray. She had first been admitted in March, 1956, for surgical treatment of leiomyomata uteri and cystic teratoma of the ovary. She dated the onset of her fatigue and weakness from that time, when a panhysterectomy with bilateral salpingo-oophorectomy and posterior vaginoplasty had been performed. She had also noted intermittent frontal headache (relieved by aspirin), palpitations, nocturia and ankle swelling after standing on her feet all day. There was no weight loss, cough, shortness of breath, dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnea, and never hemoptysis. She had been treated for essential hypertension for two years with phenobarbital, reserpine and Apresoline, with pressures ranging around 170/100 mm. of Hg. There was a history of a seizure-like episode in December, 1956, lasting two or three minutes. An electroencephalogram done at that time had shown slight cerebral impairment affecting the left hemisphere more than the right, thought to be on the basis of hypertensive

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encephalopathy. The patient stated that she had been followed in a Chest Clinic periodically since July, 1947, because of bilateral calcified densities in the chest. Films taken in 1947, 1949, 1950 and 1955 showed a slow progression of x-ray findings (figures 1 and 2). Sputum examination was consistently negative. One brother had been treated for tuberculosis in 1932. Acromegaly had been suspected in the patient in the past but ruled out on the basis of normal bone and skull films.

Physical examination at the time of admission revealed a tall, large-boned, thin Negro female in no distress. The blood pressure was 180/100 mm. of Hg; pulse,

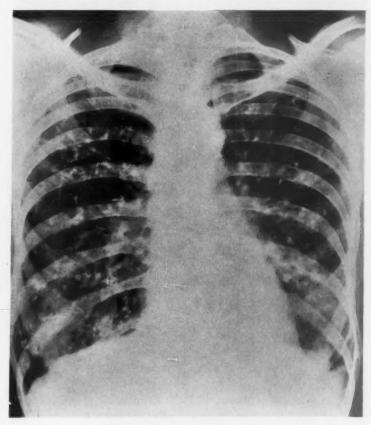


Fig. 1. Chest x-ray, July 8, 1948.

80/minute and regular. There was no cyanosis, but marked clubbing of the fingers and toes was noted. There was a slight increase in the size of the right lobe of the thyroid, which was nontender and moderately firm. Grade II arterial sclerosis was noted on funduscopic examination. The trachea was in the midline, and no adenopathy was noted. There were decreased breath sounds at the right base, with dullness to percussion in the same area. Examination of the heart and abdomen was normal.

Laboratory Findings: Hemoglobin, 13.1 gm.; hematocrit, 41%; red blood cell count, 5.31 million/cu. mm.; white blood cell count, 4,400, with 68% segmented neutrophils, 0% bands; 4% monocytes; 25% lymphocytes; 3% distintegrated cells, and slight anisocytosis. Blood urea nitrogen, 8 mg.%; total proteins, 8.45 gm.% with albumin, 5.5%, globulin, 2.9%, and A/G ratio, 1.9%. Serum cholesterol total, 294 mg.%; calcium, 9.4 mg.%; phosphorus, 3.9 mg.%. Two-hour postprandial blood sugar, 129 mg.%. Intravenous glucose tolerance test: fasting, 119 mg.%;

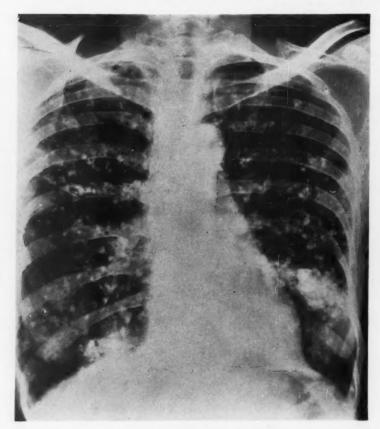


Fig. 2. Chest x-ray, March 20, 1956.

30 minutes, 183 mg.%; one hour, 183 mg.%; two hours, 127 mg.%; three hours, 76 mg.%. Urinalysis: specific gravity 1.010; alkaline; negative for sugar, albumin and sediment. Hemoglobin electrophoresis showed hemoglobin A pattern. Cerebrospinal fluid examination revealed 2 white blood cells/cu. mm.; 39 mg.% protein; clear fluid, negative Kolmer, colloidal gold curve and culture. Serologic test for syphilis was reactive in 8 dl. by Kolmer's test and in 1 dl. as performed with the Venereal Disease Research Laboratory (VDRL) antigen. Reticulocyte count. 1.0%; thrombocyte, 1.54 million; sedimentation rate (Wintrobe): observed, 46;

corrected, 34. Pleural fluid removed from the right chest was negative on routine culture, acid-fast smear and culture for fungi. Basal metabolic rate was plus 14 and plus 10. An electrocardiogram revealed an abnormal tracing, with premature ventricular beats and T wave changes indicative of nonspecific myocardial abnormality. Iodine-131 24-hour uptake, 35% retention; iodine-131 scanning revealed a functioning right thyroid nodule in the presence of a normally functioning gland. No extraglandular uptake was noted. Chest x-ray revealed pleural effusion on the right, with obstruction of the right costophrenic sulcus and right leaf of the dia-

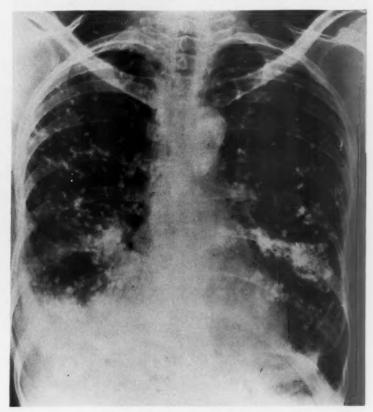


Fig. 3. Chest x-ray, May 3, 1958.

phragm. Diffuse and multiple calcifications, 5 to 15 mm. in diameter, were seen throughout both lung fields. These calcified deposits (figures 3 and 4) had radio-paque peripheries with a lucent center, and many had a small opacity within the lucent center. Comparison with outside films showed a considerable progression from 1950, with clumping in both lung fields, the process having first been seen on x-ray in 1947. A retrograde pyelogram was essentially normal with the exception of a mass in the right upper quadrant, interpreted as the liver. X-rays of the hands and feet were indicative of hypertrophic pulmonary osteoarthropathy. A skull x-ray

was negative. Skin testing: PPD #1 was positive; histoplasmin, blastomycin and coccidioidin were negative.

Hospital Course: A thoracentesis was performed for right pleural effusion. Bronchoscopy by the Chevalier Jackson Clinic was negative. An open-chest pulmonary biopsy was performed on the right side and tissue was removed for bacteriologic and histopathologic examination.

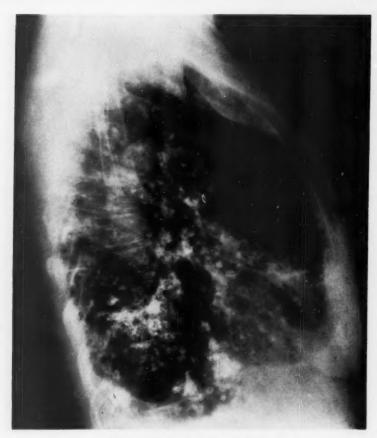


Fig. 4. Chest x-ray, May 3, 1958.

The patient continued to be asymptomatic as to pulmonary function and was discharged without specific treatment, to be followed as an out-patient.

Pathologic Report: Two wedgelike fragments of lung tissue, averaging roughly 1 cm. on a side, were submitted for histopathologic examination. Multiple sections of these submitted fragments showed an unusual and variable cyto-architecture. Generalized fibrosis affected both the pleura and the lung. The pulmonary fibrosis involved the alveolar walls and surrounded the blood vessels and lymphatics; it occurred as thin or thick septa or as nodular masses. Hemosiderin-laden macrophages

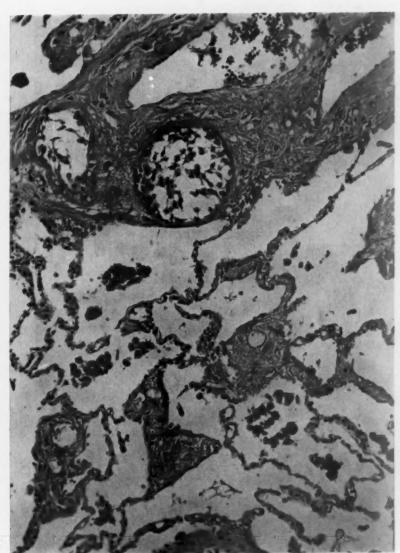


Fig. 5. Section showing thickening of the alveolar walls and perivascular and perilymphatic fibrosis, with tumor cells in lymphatic channels. × 175.



Fig. 6. Slide showing the cartilaginous nature of the tumor. X 175.

occupied the alveolar spaces. There was little vascular sclerosis, other than the striking perivascular and perilymphatic fibrous proliferation. Filling the lumina of the lymphatics were cohesive groups of tumor cells, generally with small, round nuclei and with abundant, pink-staining or clear cytoplasm (figure 5). These cells were interpreted as epithelial in nature, and a primary lesion in the kidney or thyroid was suspected. Embedded in the fibrous stroma in other areas, however, were neoplastic cells which had a cartilaginous morphology (figure 6). Foci of calcification were encountered, but there was no bone formation. Despite the chondromatous character of some of the tumor cells, we originally favored the diagnosis of metastatic carcinoma, but a primary source was not uncovered and this diagnosis failed to explain the clinical roentgen and microscopic features. Our next thought was to relate this lung picture to metastasis from a primary uterine or ovarian source. Review of these slides was not revealing. This led us to conclude that we were seeing chondrosarcomatous transformation of the pulmonary stroma. Admittedly, we have no etiologic mechanism for the pulmonary fibrosis. We postulate this came first, and then subsequently there was cartilaginous metaplastic and neoplastic change of the fibrous tissue.

## DISCUSSION

Chondrosarcoma is a relatively uncommon tumor, and is exceedingly rare in the lung. Two cases of primary chondrosarcoma in the lung have been reported. In a case described by Lowell and Tuhy 1 in 1949, such a tumor was confined to the pulmonary artery and its branches bilaterally. Diagnosis was made by histopathologic appearance rather than by evidence of extrapulmonary metastases. Death eventually occurred because of development of cor pulmonale. Greenspan 2 reported the first case of primary osteoid chondrosarcoma in 1933.

Cases have been reported of chondrosarcoma arising in distant bone and metastasizing to the lung, a extending from an obvious primary site through the inferior vena cava, heart and pulmonary arteries. Chondrosarcoma may also arise from ribs and sternum, but it rarely invades the lung secondarily.

Simon and Ballon <sup>5</sup> in 1947 described a large, discrete hamartoma which microscopically had features of malignancy, and clinically produced signs suggestive of bronchogenic carcinoma. This usually benign tumor is composed of ectodermal and mesenchymal elements, and occurs as an abnormal mixing of the normal components of the organ.

The case records of the Massachusetts General Hospital 6 contain a description of metastatic chondrosarcoma of the lung appearing 12 years after removal of osteogenic sarcoma from the region of the elbow.

### SUMMARY

A case is presented of primary chondrosarcoma of the lung of at least 11 years' duration. Extensive search for a primary site of the lung lesion, which was proved by open chest biopsy, failed to reveal an extrapulmonary source. The lesion was considered to be definitely malignant on the basis of the histopathologic features.

### ACKNOWLEDGMENT

We are indebted to Dr. Averill A. Liebow, Professor of Pathology, Yale University School of Medicine, for his consultation help on this rare and fascinating case.

### SUMMARIO IN INTERLINGUA

Es presentate un caso de probabilemente primari chondrosarcoma pulmonar de un duration de al minus 11 annos. Le patiente esseva un negressa de 53 annos de etate qui se habeva hospitalisate con le gravamine de fatiga chronic e a causa de anormalitates del roentgenogramma thoracic. Le roentgenogramma del thorace revelava calcificationes bilateral con centros de radiolucentia in le parenchyma. Le constatationes roentgenographic habeva progredite lentemente depost 1947. Un fonte primari de sito extrapulmonar non poteva esser trovate. Esseva effectuate biopsia pulmonar a thorace aperte, e le specimen obtenite esseva examinate bacteriologicamente e histopathologicamente. Fibrose pulmonar esseva vidite, le plus frappantemente in le areas perivascular e perilymphatic. Gruppos cohesive de cellulas epithelial replenava le lumines del vasos lymphatic. In altere areas de stroma fibrose, cellulas neoplastic con morphologia cartilaginose esseva observate, con focos de calcification sed sin formation de osso. Es opinate que isto representa un transformation chondrosarcomatose de stroma pulmonar, imponite super fibrose pulmonar, sed nos debe admitter que pro iste ultime nos non pote citar un etiologia. Duo previe casos de primari chondrosarcoma pulmonar se trova reportate in le litteratura. Le presente caso es le tertie. Nulle tractamento specific pote esser recommendate al presente pro iste condition. Le lente progresso e le constatation de cellulas neoplastic duce a interessante speculationes con respecto a un possibile etiologia,

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# **EDITORIALS**

MAURICE C. PINCOFFS, EDITOR OF THE ANNALS

For the first time in twenty-seven years an issue of the *Annals of Internal Medicine* appears without the name of Maurice C. Pincoffs at the masthead. His period of editorship has been long and fruitful, so much so that the *Annals* and Dr. Pincoffs have come to have a single identity. For this long and honorable service the American College of Physicians and the readers of the *Annals* owe him an immeasurable debt of gratitude. To Maurice C. Pincoffs, retiring Editor, this issue of the *Annals* is dedicated.

Elsewhere in this issue an account is given by a friend and peer of Dr. Pincoffs' career as Editor of the *Annals* and as a leader in the American College of Physicians. To the Editor who has succeeded him, however, Dr. Pincoffs' accomplishments are especially impressive if not frightening. Twenty-seven years after undertaking the editorship and some nine thousand manuscripts later, Dr. Pincoffs can retire with the sure knowledge that he has made the *Annals* one of the outstanding medical journals of the world. This has been no small burden carried, this has been no slight goal attained.

In the first issue of the *Annals* under his editorship Dr. Pincoffs set forth his editorial policy and his criteria for selection of manuscripts. He stated that one of the functions of the *Annals* was to publish noteworthy addresses and clinics delivered at the annual meeting of the College, that another was to publish scientific papers submitted directly to the Editor. Concerning these he said, "Naturally the first selection will be based on quality. The completeness of data, the reliability of methods, the considerations given to the work of others, the proof offered in support of assertions should all be weighed before a manuscript is accepted." He went on to state that priority would be given to subjects most directly within the scope of internal medicine, a field which he defined broadly as blending "into all the medical sciences and all the clinical specialties." Thus Maurice C. Pincoffs laid the ground rules and the goals for his editorship; the succeeding twenty-seven years testify both to their excellence and to their ample fulfillment.

No consideration of the retiring editorship would be complete without mention of other members of the editorial team. Dr. Paul W. Clough, Associate Editor, has long supported Dr. Pincoffs in his editorial tasks; especially notable have been Dr. Clough's excellent and thorough editorial reviews of many subjects in the field of internal medicine. Dr. Fred R. McCrumb, Jr., Assistant Editor, has provided editorial help in more recent years. And honors are especially due to two ladies in the *Annals* office for their able and faithful handling of the editorial mechanisms that month by month have produced the *Annals of Internal Medicine*. These are Mrs. Benton B. Westfall, who has been in the Editor's office for all the years of

Dr. Pincoffs' editorship, and Mrs. Harold S. Goodwin, who has completed her thirteenth year of service. To these Editorial Assistants has fallen much of the exacting work of preparing manuscripts, their illustrations and their bibliographies for the printer, as well as the scrupulous reading of the proofs. To these members of Dr. Pincoffs' team, and to Dr. Pincoffs himself, all who are concerned with the Annals may say, "Well done, we salute you!"

I. R. E.

## HEPATIC COMA

NEUROPSYCHIATRIC disturbances progressing at times to actual coma have been recognized for many years as a not infrequent complication of the terminal stages of cirrhosis. In fact excerpts from medical writers of antiquity have been quoted as possibly descriptions of such a condition. It has been recognized for many years that this "hepatic coma" was quite distinct from uremic and diabetic coma and that it was not associated with intracranial lesions or other generally recognized causes of such psychic disturbances. Until recently, however, nothing precise was known regard-

ing its pathogenesis.

The first major lead to an understanding of this condition seems to have been obtained from a study of the experiments of Pavlov and his associates (1893) on dogs on which a portacaval anastomosis (Eck fistula) had been carried out. In general such dogs usually recovered and remained in a fair state of health although some degree of atrophy of the liver and some impairment of function eventually occurred. Pavlov showed that if these dogs were fed a meat diet an intoxication occurred characterized by lethargy, hypotonia, weakness, ataxia, salivation, stupor and even fatal convulsions, symptoms resembling those observed in human cases of hepatic coma. This intoxication has subsequently been attributed to the absorption of nitrogenous products resulting from the breakdown of protein in the intestine, which have bypassed the liver and have not been normally metabolized.

The symptoms of hepatic coma and of impending coma have been frequently described, and in especial detail by Summerskill et al.1 who credit Adams and Foley with the first adequate description. Summerskill's report was based upon a study of 17 patients, 16 with cirrhosis of the liver and one with a traumatic stricture of the bile duct. The disturbances come in recurring attacks, "episodic stupor," at irregular intervals, often after a liberal intake of protein, they reach a maximum after one or two days, and more gradually subside.

The earlier stages are marked by changes in personality, mental confusion, lethargy, sometimes by irritability or violence if aroused, by abnor-

Summerskill, W. H. J., Davidson, E. A., Sherlock, S., and Steiner, R. E.: The neuro-psychiatric syndrome associated with hepatic cirrhosis and an extensive portal collateral circulation, Quart. J. Med. 25: 245-266, 1956.
 Adams, R. D., and Foley, J. M.: Neurological disorder associated with liver disease, A. Res. Nerv. and Ment. Dis., Proc. (1953) 32: 198-237, 1953.

malities of speech and by various motor disturbances. There is often uninhibited behavior, personal untidiness, grossly inappropriate actions, confusion as to time and place. A patient may get lost in his own house, may be unable to dress, may try to shave with his tooth brush. Mental processes are slowed, there is apathy, reduced spontaneous movements, a meaningless stare, unresponsiveness or slow abbreviated responses, with slurred speech, dysphasia, and perseveration. This may progress to profound coma, with muscular rigidity, fetal attitudes and stertorous breathing. Convulsions rarely occur. Complete recovery after a few days is the rule.

The motor disturbances include clumsiness, ataxia, disruption of voluntary movement, dropping of articles, apraxia, very tremulous writing with omissions, misspelling and eventually disorganization, tic-like movements, blinking, and grimacing. There is often salivation. The muscles are commonly hypertonic, the deep reflexes exaggerated with an ankle clonus, but usually flexor plantar responses. The combination of symptoms indicating disturbances of both pyramidal and extrapyramidal tracts with normal plantar reflexes has been stressed, but in deep coma the muscles may become flaccid and the plantar response extensor.

There is often also a peculiar "flapping" tremor which has been emphasized as highly characteristic although not pathognomonic of impending hepatic coma. It is a slow coarse tremor initiated or increased by sustained muscular effort. It is commonly demonstrated by having the subject stand with arms stretched forward and extended at the elbows, wrists and fingers. In milder cases the tremor is manifested by alternate flexion and extension of the metacarpophalangeal joints. In more severe cases similar movements may occur at the wrists and elbows also. As the extension is carried out slowly and the flexion more rapidly, it gives the impression of flapping.<sup>3</sup>

These attacks, including the mental disorders, usually clear up completely without any permanent defect. They have been observed recurring repeatedly over a period of two to three years without sequelae. They are regarded as "organic"; not functional in the sense of being primarily emotional in origin. In predisposed subjects, however, an attack of coma may release a functional psychosis, such as a depressive, compulsive, or schizophrenic reaction. Four of Summerskill's cases were initially admitted to mental hospitals. The attacks are attributed to a metabolic (chemical) derangement, not to any demonstrable anatomical lesion of the nervous tissue. In some cases there has been extensive proliferation of astrocytes with marked enlargement of these cells, Alzheimer's type II glial cells, but these also are not specific and appear inadequate to explain the neurologic symptoms.<sup>2, 4</sup>

<sup>4</sup> Sherlock, S.: Pathogenesis and management of hepatic coma, Am. J. Med. 24: 805–813, 1958.

<sup>&</sup>lt;sup>8</sup> Phillips, G. B., Schwartz, R., Gabusda, G. J., Jr., and Davidson, C. S.: The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances, New England J. Med. 247: 239-246, 1952.

Electroencephalographic changes occur during the attacks, bursts of slow waves of high amplitude, starting bilaterally in the frontal regions and in severe cases becoming generalized. The tracings usually revert toward normal during the remissions.

The degree of impairment of liver function varies, but as determined by the usual tests it may be relatively slight. A practically constant finding of primary importance, however, is evidence of shunting of blood from the portal vessels directly into the systemic circulation.1,4 This is frequently through collateral vessels which are enlarged as a result of high pressure in the portal system. The latter may result from intrahepatic obstruction due to cirrhosis or it may be due to thrombosis or other mechanical occlusion of the portal vein itself. The collateral vessels may be within the liver if fibrosis is extensive. The shunt may be produced deliberately by operation to relieve intractable ascites or esophageal varices or to facilitate extensive resections of cancerous tissue. More rarely the same result may ensue if the hepatic tissue has been almost completely destroyed by some acute process such as a viral hepatitis. The blood may then circulate through the liver in the usual channels but uninfluenced by the nonfunctioning hepatic cells.<sup>5</sup> Otherwise the precise degree of impairment of hepatic function has little or no relation to the attacks of coma.1

Much study has been devoted to identifying the toxic substance in the blood that causes these reactions. Suspicion has been directed especially to ammonium which is the simplest of the nitrogenous breakdown products, and attempts have been made to determine the quantity of this substance in the blood. This has met with technical difficulties. The quantities involved are minute, in normal blood in the range of 50 to 100 micrograms per 100 ml., varying with the method used. There is, however, no absolute proof that the substance being measured ("volatile base") is actually ammonium or at least that all of it is. Furthermore the quantity present, as determined by these tests, increases progressively after the blood is shed, and there are reasons for believing that there is actually no detectable amount free in the circulating blood. The measurable amount increases relatively rapidly during the first three minutes, presumably as it is liberated from the amino acids or other breakdown products, and then much more slowly. The amount present after three minutes has been arbitrarily selected by some investigators as the best measure of the blood "ammonium" now available.6

Bearing in mind these doubts as to specificity and precision, the blood "ammonium" in the systemic vessels of normal individuals is about 40 to 60 (possibly 100) micrograms per 100 ml. and not notably different in arterial

<sup>&</sup>lt;sup>5</sup> Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A.: Portal-systemic

encephalopathy. Neurological complications of liver disease, Lancet 2: 453, 1954.

<sup>6</sup> White, L. P., Phear, E. A., Summerskill, W. H. J., and Sherlock, S.: Ammonium tolerance in liver disease: observations based on catheterization of the hepatic veins, J. Clin. Investigation 34: 158-168, 1955.

and venous blood. It is higher in the portal vein but reduced in the hepatic vein after passage through the liver.

In patients with cirrhosis who are not severely ill, the ammonium levels in the fasting state are approximately normal. If there is food (protein) in the intestine, the ammonium in the portal vein will rise sharply. The levels in the other vessels will depend largely upon the extent of the collateral circulation and to some extent upon the degree of functional injury of the hepatic cells. If an effective shunt has developed, the ammonium in the systemic vessels will rise as portal vein blood bypasses the liver. It is usually higher in the artery than in the vein. There may be a further rise in patients showing manifestations of impending or actual coma. In patients who are subject to such attacks, one may be precipitated by feeding protein, and this is usually accompanied by a sharp rise in blood ammonium. A similar result may follow the oral administration of ammonium chloride, diammonium citrate, methionine or urea.<sup>a</sup>

As pointed out by White et al., ammonium answers most of the requirements of the toxic substance. It is readily absorbed, and its concentration rises rapidly in the portal vein. It can enter the general circulation in large amounts through collateral vessels, and it is toxic. There is at least a reasonable correlation between the severity of the neuropsychiatric symptoms and the average arterial ammonium levels, but with much overlap and many exceptions. It is generally agreed that "a direct quantitative and temporal relationship does not exist." <sup>7, 8</sup> Ammonium alone can not adequately account for the observations.

What the toxic substance is has not been determined. Amino acid mixtures, especially if unbalanced, are also toxic. Fahey, e.g. reported that the intravenous administration of a mixture containing all the "essential" amino acids (but no arginine) caused a toxic reaction resembling hepatic coma in three of seven subjects severely ill with cancer, who were unable to take any food by mouth. This was accompanied by a sharp rise in blood ammonium. A similar rise occurred when glycine was administered. It is therefore possible that ammonium may participate with some other breakdown product in producing this reaction, or it may be a fairly constant indicator of some other unidentified toxic substance. Blood pyruvate and  $\alpha$ -ketoglutarate are increased in hepatic coma. The latter may combine with ammonium to form glutamic acid and glutamine. This removes some of the excess ammonium, but it eliminates one constituent of the Krebs citric acid cycle (aerobic glycolysis) which constitutes a major source of energy for brain tissue. This theory receives some confirmation from the fact

 $<sup>^7</sup>$  Summerskill, W. H. J., Wolfe, S. J., and Davidson, C. S.: The metabolism of ammonia and  $\alpha$ -keto acids in liver disease and hepatic coma, J. Clin. Investigation 36: 361–372, 1957.

Seegmiller, J. E., Schwartz, R., and Davidson, C. S.: The plasma "ammonia" and glutamine content in patients with hepatic coma, J. Clin. Investigation 33: 984-988, 1954.
 Fahey, J. L.: Toxicity and blood ammonia rise resulting from intravenous amino acid administration in man, J. Clin. Investigation 36: 1647-1655, 1957.

that arginine, which is believed to participate in the process of converting ammonium to urea in the Krebs cycle, will prevent the toxic reaction and the associated rise in ammonium if administered with the amino acid mixtures.9

The clinical picture of hepatic coma can be produced in subjects without serious hepatic disease if portal vein blood is entirely shunted into the general circulation. Such a case has been reported by McDermott et al., 10 a patient who had an extensive resection of a pancreatic carcinoma, during the course of which the superior mesenteric vein was anastomosed to the inferior vena cava. This was followed by periods of "episodic stupor," accompanied by "precipitous elevations of the blood ammonium." This was relieved by a low protein diet, under 40 grams a day. Attacks were precipitated by a high protein diet, by administration of ammonium chloride or an ammonium cation exchange resin. One particularly profound attack was produced by the administration of urea, which was followed by intellectual impairment lasting several weeks. At necropsy somewhat later, fatty infiltration of the liver was found, but no cirrhosis. Magnum et al.11 reported a somewhat similar case. Attacks of coma of appreciable severity have been reported in 10 to 20% of patients with an Eck fistula and in some series in milder forms up to 30%.1 Dogs with an Eck fistula also have high blood ammonium during meat intoxication.

Zieve et al.12 have reported three cases with a portacaval shunt in which intolerance to protein progressed to the point where they could not tolerate more than 20 grams of protein per day, a quantity insufficient to prevent progressive loss of weight and wasting of the body stores of protein.

Although in general no associated organic lesions in the nervous system have been recognized, other than proliferation of astrocytes, in two of these cases a permanent bilateral spastic paraplegia developed. 13 In the one that came to necropsy, there was extensive demyelination of the pyramidal tracts in the spinal cord but intact axones. They found two somewhat similar cases previously reported with demyelination of the tracts in the spinal cord and areas of spongy degeneration with loss of nerve cells scattered in the cortex and basal ganglia.

Treatment of an individual attack is usually fairly effective—a low protein or protein-free diet, glucose infusions, cathartics and oral administration of broad-spectrum antibiotics such as neomycin to lessen breakdown of protein by bacterial growth in the intestine. Hemorrhage into the gastro-

<sup>&</sup>lt;sup>10</sup> McDermott, W. V., Jr., and Adams, R. D.: Episodic stupor associated with an Eck fistula in the human with particular reference to the metabolism of ammonia, J. Clin. Investigation 33: 1-9, 1954.

vestigation 33: 1-9, 1954.

11 Magnum, J., Lamons, D., and Friedlander, W. J.: Neurologic changes in a patient with portacaval shunt and the relationship to hepatic coma, Am. J. Med. 21: 306-311, 1956.

12 Zieve, L., Mendelson, D. F., and Goepfert, M.: Shunt encephalomyelopathy. I. Recurrent protein encephalopathy with response to arginine, Ann. Int. Med. 53: 32, 1960.

13 Zieve, L., Mendelson, D. F., and Goepfert, M.: Shunt encephalomyelopathy. II. Occurrence of permanent myelopathy, Ann. Int. Med. 53: 53, 1960.

intestinal tract is particularly disturbing and when present requires energetic

Injections of arginine have also been used on the basis of its beneficial effects in man and animals, when unbalanced amino acid mixtures or ammonium salts are administered. Najarian 14 reported good results in 15 cases following intravenous injection of 50 to 100 grams. Fahey 15 and Reynolds et al.,16 however, were less impressed, as was also Sherlock.4 Several favorable reports have since been published, notably by Zieve et al., 12 who used it with usually favorable results in 40 cases of hepatic coma. They obtained "a significant number of unequivocal responses," particularly "in patients who are frankly unconscious with hepatic coma due to an exogenous cause." They point out that arginine can not be expected to cure the underlying disease or avert an eventually fatal outcome but at best to terminate or shorten an existing period of coma. The dose is also critical, at least 50 to 100 grams usually being necessary. In many of the failures smaller doses had been used. The effect is not immediate, but often evident only after 12 to 24 hours. The results were particularly striking in the three cases with very low protein tolerance who suffered repeated attacks of coma. Other metabolic disturbances or deficiencies may coexist, particularly of potassium and magnesium, and also require correction.

Although attacks of hepatic coma often show certain peculiar and characteristic clinical features, they can not always be differentiated with certainty from other metabolic and neuropsychiatric disorders. Points which should arouse suspicion are the episodic recurrence of attacks, without sequelae in the intervals; the onset with peculiar psychic disturbances—a change in personality, retardation of mental processes, confusion, disorientation, noisy delirium, and clumsiness of movement, slurred speech and the flapping tremor. The appearance of slow waves of high amplitude in the electroencephalogram is characteristic. Also confirmatory is demonstration of chronic disease of the liver and particularly evidence of collateral portacaval circulation, an enlarged spleen and a high blood ammonium if means for determining this are available. The precipitation or aggravation of an attack by feeding protein and the more slowly demonstrable benefit from a protein-free diet are highly significant. No test is diagnostic and much depends upon experience and critical clinical judgment. The problem is more than academic, since therapeutic measures of considerable value are available.

PAUL W. CLOUGH, M.D.

Najarian, J. S., and Harper, H. A.: A clinical study of the effect of arginine on blood ammonia, Am. J. Med. 21: 832-842, 1956.
 Fahey, J. L., Nathans, D., and Rairigh, D.: Effect of 1-arginine on elevated blood ammonia levels in man, Am. J. Med. 22: 860-869, 1957.
 Reynolds, T. B., Redeker, A. G., and Davis, P.: A controlled study of the effects of 1-arginine on hepatic encephalopathy, Am. J. Med. 25: 359-367, 1958.

# **BOOK REVIEWS**

Leukaemia: Research and Clinical Practice. By F. G. J. Начное, М.А., М.D. (Cantab.), М.R.C.Р. (Lond.) 335 pages; 25.5 × 19.5 cm. Little, Brown and Co., Boston. 1960. Price, \$16.00.

The author of this new monograph has skillfully synthesized and marshalled a vast body of data concerning leukemia. Research and clinical aspects are reviewed clearly and concisely. Each section is buttressed by an extensive and up-to-date bibliography. The cytology, cytochemistry, biochemical, tissue culture, and immunologic aspects of the leukemic cell are discussed. Where necessary for subsequent discussion, brief expositions of the fundamentals of nucleoprotein metabolism, glycolysis, and cellular respiration are presented. Clinical aspects and general principles of therapy occupy approximately half the book. The mode of action and particular areas of usefulness of various groups of chemotherapeutic agents are fully covered. Included is a concise basic discussion of the biologic effects of ionizing radiation. The book is well illustrated by many excellent photomicrographs and a number of color plates which are perhaps less precise in representation. It will serve well as a reference source for workers in the field as well as for those more casually concerned with these problems who seek authoritative views. Although there are no new concepts here, the extensive and careful collecting of data may in itself provide further stimuli and inspiration for the ultimate control of leukemia. The book can be highly recommended.

MILTON S. SACKS

Electrophysiology of the Heart. By Brian F. Hoffman, M.D., and Paul F. Cranefield, Ph.D. 323 pages; 22 × 14.5 cm. The Blakiston Division, McGraw-Hill Book Co., New York, N. Y. 1960. Price, \$12.50.

The technic of single-cell recording of action potentials serves as the basis for this book on electrophysiology of the heart. Although the method is only 10 years old, a significant literature has accumulated. The present text presents the results of this work, including the significant contributions by the authors and others. A good deal of the data has not been previously published.

After the initial chapters on recording technics and excitation and conduction, succeeding chapters are devoted to the action potentials of the atrium, ventricle, sinoatrial node, atrioventricular node, Purkinje fibers and excitability. The last chapter, "General Electrophysiology of the Heart," contains a critical presentation

of a possible ionic mechanism for repolarization.

Although this text is primarily concerned with action potentials of single cardiac cells, the discussions go beyond the single cell and include much which should be of use to those interested in electrocardiography. As the authors state in the Preface, "The electrocardiographic record of the electrical activity of the whole heart depends upon the shape of the action potentials of the various cells of the heart and upon the sequence of activation of those cells." The effects of temperature, various ions, the vagus, acetylcholine, epinephrine, and other factors are reported. Critical discussions and differing opinions are presented.

This book represents a significant contribution in the field of electrophysiology. It should prove of interest not alone to physiologists but to the serious student of

electrocardiography.

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Anorexia Nervosa: Its History, Psychology, and Biology. A Psychosomatic Medicine Monograph. By Eugene L. Bliss, M.D., and C. H. Hardin Branch, M.D. 210 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York, N. Y. 1960. Price, \$5.50.

Any physician who has struggled with the complicated problem of understanding and treating a patient with anorexia nervosa will acclaim this volume as an important, concise and scholarly contribution. The central issue of this book is the presentation of a resumé of the pertinent psychiatric and medical studies of 22 cases of anorexia nervosa, or what the authors call "psychogenic malnutrition." The chapters consider in sequence the following subjects: the historical aspects, the clinical aspects, the psychodynamics, the biology and the treatment of this condition. These are followed by a chapter on the individual protocols of the 22 cases, carefully analyzed and succinctly presented by the authors. An excellent bibliography is included, which should serve as an important source of reference for anyone who desires to search the literature on this subject.

Anorexia nervosa occurs more frequently than is usually supposed, and this becomes even more apparent when one considers the mild or moderate form of this illness, which is not recognized for its true nature. The authors contend that this condition (of diminished caloric intake) is a symptom-complex found at times in almost all psychiatric categories, and may indicate either an underlying neurotic or a psychotic personality deviation.

The theoretic underlying psychopathology of this condition is presented well and in a common-sense manner, and an unbiased approach is maintained in explaining the psychogenesis of this illness. The authors carefully avoid being dogmatic, and offer a readable and understandable account of the various schools of thought concerning this point. The thesis is offered that the cumulative impact of many successive events, both early and late in the life history of the patient, and focusing upon the area of food, obesity and digestion, appears to be a critical factor.

The weight loss which occurs in this condition leads to many biochemical and physiologic changes. The authors contend that the hypopituitarism secondary to the malnutrition causes a partial or complete gonadotropic insufficiency and thus gonadal failure. However, they argue against the opinion that this same hypopituitarism has a direct inhibiting effect on the function of the thyroid and adrenal glands. The reviewer respectfully submits that he has studied cases of anorexia nervosa where it seemed rather definite that the diminished function of the thyroid gland was not only a function of the general compensatory hypometabolism of the semi-starved patient, as the authors of this book contend, but that this target gland was also directly affected by the hypopituitarism, just as are the gonads.

In considering the treatment of anorexia nervosa, the authors deplore the use of endocrine replacement, and focus rather on the following two important areas: first, the major and, at times, emergency problem of treating the malnutrition; second, the less immediately urgent but even more taxing problem of treating the psychologic disturbance responsible for it. They discuss the many variations in technic of both somatic therapy and psychotherapy that have been used. They recommend the consideration of certain logical general principles; however, they maintain that the ultimate decision as to the appropriate treatment will depend upon both the basic psychologic disturbance of the individual and the degree of malnutrition.

A word of caution: both organic hypopituitarism and pinealoma have on rare occasions been known to resemble the clinical picture of classic anorexia nervosa.

This illness, which is associated with a remorseless drive toward self-starvation, is a continuing challenge to medical practice. This book is an important contribution to its understanding and is highly recommended by the reviewer as a worth while addition to the library of both the internist and the psychiatrist.

Medical Physiology and Biophysics. Edited by Theodore C. Ruch, Ph.D., and John F. Fulton, M.D. 1232 pages; 26 × 17.5 cm. W. B. Saunders Company, Philadelphia. 1960. Price, \$16.00.

This is really the eighteenth edition of "Howell's Physiology," which has probably been used by more American medical students than any other physiology text. The fifteenth, sixteenth and seventeenth editions were edited by Dr. John F. Fulton, and he has collaborated with Dr. Ruch in editing the present edition.

This is a much different sort of book from the original "Howell," which was largely the work of one man. Fulton, in three previous editions, and now Ruch and Fulton, have chosen to present a book whose chapters have been written by a group of physiologists. Thanks to expert assistance from these collaborators plus good editing, this is a coherent, unified textbook rather than a collection of monographs.

In the preface, Dr. Ruch outlines his conviction that physiology should be developed and taught "in depth" by ranging from the fundamental disciplines of physics and mathematics, through classical physiology, to clinical physiology. Although most would agree with this point of view, the book does a much better job of presenting fundamentals and classical physiology than it does in its presentation of clinical physiology. This is probably related to Dr. Ruch's choice of authors: Of the 23 persons who have written, or revised, the various chapters, seven are physicians; the others, Ruch included, do not have a medical degree. As a result, most of the articles either do not attempt to present "clinical physiology" or, when they do, the naïveté is obvious.

Since this book is presumably intended for use by students, it has a serious defect: The references do not list titles of articles referred to. In a specialty journal, such as *The American Journal of Physiology* or the *Journal of Biological Chemistry*, such a procedure is understandable. The additional cost is not justified since readers are familiar with most of the references plus the fact that a relatively short list of readily available journals makes up most of the sources. The situation, however, is quite different in a textbook—especially physiology, which is too large a field for any one book. Students of all ages should be provided with as much help and as much stimulus for further study as the editors and the publishers can give them. One form of such assistance is to include the full title of references. Even better, but rarely seen, is an editorial comment on the articles.

The publisher is probably responsible for another, much less important, defect: The index, instead of using bold face type to indicate the page number of tables or figures, uses italics which can hardly be distinguished from the type used for regular numbers.

As implied earlier, this is a textbook of classical "Ph.D. Physiology," not "Medical Physiology." As such, it is as up-to-date and as authoritative as expert physiologists and dynamic editing can make it. Old chapters have been discarded and new ones prepared especially for this edition; almost all other chapters, prepared for the previous edition, have either been revised, rewritten, or edited by, a credit line being given the new author so that there is no doubt about who wrote what and when.

Two new chapters have been added: one on the Biophysics of the Cell Membrane; another on the Neurophysiology of Emotion and Motivation. The first of these chapters is very good; the subject should be covered even more fully in the next edition. The chapter on the Physiology of Emotion is a brave effort, but in a text-book of Medical Physiology it needs the perspective of a physician in addition to the mechanistics of a physiologist.

Gestation: Transactions of Fifth Conference, March 11, 12, and 13, 1958, Princeton, N. J. Edited by Claude A. Villee, Ph.D. 262 pages; 24 × 16 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. 1959. Price, \$5.75.

This is a verbatim report of the fifth yearly conference sponsored by the Josiah Macy, Jr. Foundation. Following the procedure of the previous conferences, distinguished basic science authorities and clinicians who share a reputation for their investigations into the multi-faceted problems related to gestation have been brought together for purposes of uninhibited discussion and criticism of their current research projects in this broad field of interest.

This report represents a gold mine of related information pulled together and organized from observations made in many fields of investigation. The list of topics is varied and includes discussions of the venous drainage of the uterus, circulation of the placenta, recent studies of the Rh factor, and effects of physiological stresses on fetal circulation, to name just a few. To have these subjects presented by the men who are currently most active in the field and discussed by leading authorities in this field is as much as one could ask of any book. Illustrations, printing, and pertinent bibliographies are excellent.

RICHARD S. MUNFORD

Thoracic Surgery before the 20th Century. By Lew A. Hochberg, M.D. 858 pages; 23.5 × 16 cm. Vantage Press, Inc., New York, N. Y. 1960. Price, \$15.00.

The source material used by Dr. Hochberg to produce this fascinating account of Thoracic *Medicine* (as well as Surgery) before the 20th century has been collected and studied by him during some 20 years. It covers much more than the surgical side of the story. There are many interesting bypaths: Hutchinson's studies of the vital capacity; Roentgen's tribulations with credit for priority for his discovery; Lister's trouble with Sir James Simpson; a too short piece about J. B. Murphy, and many others. The parts are skillfully interwoven, and the result is a fascinating account of a large segment of medical history which seems to gain interest because of Dr. Hochberg's knowledge of both the historical and the day to day labor side of the subject.

Unfortunately, the publisher has chosen to use a grade of paper and a reproduction process that do the illustrations an injustice; this is the book's only fault among many virtues. Dr. Hochberg is working on a companion volume, A Source Book of Thoracic Surgery in the 20th Century. If sales of the present volume parallel its worth, the publisher should try to give more attention to the quality of illustrations in the new volume.

B. W. A.

Medieval and Renaissance Medicine. By Benjamin L. Gordon, M.D., F.I.C.S. 843 pages; 14.5 × 21.5 cm. Philosophical Library, New York. 1959. Price, \$10.00.

"Medieval" and "Middle Ages" as designations of segments of time in history seem to be somewhat interchangeable and overlapping. Medieval is referred to as that span from 500 A.D. to 1500 A.D.; Middle Ages is the name given to the period of European history that followed ancient times and preceded modern times, approximately from the fall of Rome (476 A.D.) to 1500 A.D. The Renaissance delineates the time of the great revival of art, literature and learning in Europe in the 14th, 15th and 16th centuries which marked the transition from the medieval to the modern world. Thus, the author has undertaken the prodigious task of describing and

interpreting the medical events which took place from the fall of Rome to the end of the 16th century. That any physician found the time necessary to do this is a wonder to this reviewer.

Errors of the proofreader have done the author a great disservice since they abound in countless misspelled words and proper names. These errors somewhat detract from the enjoyment of reading the text as discords detract from listening to music

The author brings the reader down to date by describing events in medical history which led to an understanding of the cause of disease and then its elimination by modern methods of the present. He also gives his own interpretations of the physical and emotional effects on the populace of the great epidemics, the Crusades, and the environmental, social, economic, political, religious, and educational influences of the times.

Along with the other forms of awakening which characterized the Renaissance, the author observes that, "The spirit of experimentation dawned in the Renaissance" and, "The renaissance of medicine began with anatomy." He concludes with the observation, "If the Renaissance did not achieve the aim medicine was striving for (for indeed the science of medicine is endless), it served as the means to rid the art and science of medicine from much of the rubbish that had accumulated throughout the ages."

This book should be of value to historians and students of the period, and to those who enjoy medical history as recreational reading.

J. E. S.

#### BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Actualités Néphrologiques de l'Hôpital Necker, 1960. Clinique des Maladies, Professeur J. Hamburger. 278 pages; 25 × 16 cm. 1960. Editions Medicales Flammarion, Paris. Price, 49,50 NF + T.L
- Bedside Diagnosis. 5th Ed. By Charles Seward, M.D., F.R.C.P. (Edin.), Physician, Royal Devon and Exeter Hospital, etc. 479 pages; 19 × 12.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$6.00.
- J.-M. Charcot, 1825–1893: His Life—His Work. By Georges Guillain, M.D., Membre d'l'Institut, Membre de l'Académie de Médecine; edited and translated by Pearce Bailey, Ph.D., M.D., Director, National Institute of Neurological Diseases and Blindness, etc. 202 pages; 21.5 × 14.5 cm. 1959. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$7.00.
- Classification of Pharmaceutical Preparations: A Survey of Existing Legislation. (Originally published in the International Digest of Health Legislation, 1960, 11: 4-56.) 56 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.
- Confidentiality and Privileged Communication in the Practice of Psychiatry, Formulated by the Committee on Psychiatry and Law, Group for the Advancement of Psychiatry. Report No. 45, June, 1960. 25 pages; 23 × 15 cm. (paper-bound). 1960. Group for the Advancement of Psychiatry, New York. Available at 50¢

- each, quantity rates upon request to Publications Office, Group for the Advancement of Psychiatry, 104 East Twenty-fifth Street, New York-10.
- Disease and the Advancement of Basic Science. Edited by Henry K. Beecher. 416 pages; 24 × 16 cm. 1960. Harvard University Press, Cambridge. Price, \$12.50.
- Diseases of the Newborn. By Alexander J. Schaffer, M.D., Associate Professor of Pediatrics, The Johns Hopkins Medical School, and Pediatrician to The Johns Hopkins Hospital, etc.; with a Section on Neonatal Cardiology by Milton Markowitz, M.D., Assistant Professor of Pediatrics, The Johns Hopkins Medical School, and Pediatrician to The Johns Hopkins Hospital, etc. 878 pages; 26 × 17.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, \$20.00.
- Einführung in die innere Medizin. By Dr. Hans Julius Wolf. 751 pages; 24.5 × 17.5 cm. 1960. Georg Thieme Verlag, Stuttgart; available in U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. Price, \$10.00.
- Electrocardiography: Principles and Practice. By Ernest Bloomfield Zeisler, M.D., Clinical Associate Professor of Medicine, Chicago Medical School. 374 pages; 29 × 22 cm. 1960. Login Brothers, Chicago. Price, \$12.50.
- The Heart in Industry. By TWENTY-FOUR AUTHORS; edited by LEON J. WARSHAW, M.D., F.A.C.P., Consultant in Occupational Health, etc.; foreword by IRVING S. WRIGHT, M.D. 677 pages; 24 × 16.5 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. Price, \$16.00.
- Highlights of Research Progress in Allergy and Infectious Diseases, 1959. Items of Interest on Research Studies Conducted and Supported by the National Institute of Allergy and Infectious Diseases. Prepared by the National Institute of Allergy and Infectious Diseases as Background Material for Submission at Congressional Hearings on Appropriations for Fiscal Year 1961. Public Health Service Publication No. 745. 53 pages; 23.5 × 15 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda 14, Maryland. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢.
- Industrial Pulmonary Diseases: A Symposium held at The Postgraduate Medical School of London, 18th-20th September, 1957 and 25th-27th March, 1958. Edited by E. J. King, M.A., D.Sc., F.R.I.C., Postgraduate Medical School of London; and C. M. Fletcher, C.B.E., M.D. (Cantab.), F.R.C.P., Postgraduate Medical School of London. 269 pages; 22.5 × 14.5 cm. 1960. Little, Brown and Company, Boston. Price, \$8.50.
- Internal Medicine: A Physiologic and Clinical Approach to Disease. 2nd Ed. By ROBERT P. McCombs, B.S., M.D., F.A.C.P., Professor of Graduate Medicine, Tufts University School of Medicine, etc. 750 pages; 23.5 × 15.5 cm. 1960. The Year Book Publishers, Chicago. Price, \$10.50.
- Intra-osseous Venography. By Robert A. Schobinger, M.D., Clinical Instructor in Surgery, Albert Einstein College of Medicine, New York, N. Y., etc. 243 pages; 18 × 25.5 cm. 1960. Grune & Stratton, New York. Price, \$14.50.
- Manual for Examination of Patients. FACULTY COMMITTEE, KERR L. WHITE, M.D., Chairman. School of Medicine and North Carolina Memorial Hospital,

- The University of North Carolina, Chapel Hill, N. C. 231 pages;  $19\times11.5$  cm. (paper-bound). 1960. The Year Book Publishers, Inc., Chicago. Price, \$4.50.
- Medical Physiology and Biophysics. 18th Ed. of Howell's Техтвоок оf Physiology. Edited by Theodore C. Ruch, Ph.D., Professor and Executive Officer, Department of Physiology and Biophysics, University of Washington School of Medicine; and John F. Fulton, M.D., Sterling Professor of the History of Medicine, Yale University School of Medicine. 1,232 pages; 26 × 17.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, \$16.00.
- Medicinal Plants of the Arid Zones (Arid Zone Research—XIII). 96 pages; 24 × 15.5 cm. (paper-bound). 1960. United Nations Educational, Scientific and Cultural Organization, Paris. Price, \$3.00.
- Medicine for Dental Students. By R. A. CAWSON, M.B., B.S., B.D.S., F.D.S., R.C.S. Eng., Senior Lecturer in Oral Pathology, King's College Hospital Medical School (University of London) Dental School, etc.; and R. H. CUTFORTH, M.D., M.R.C.P., Physician Specialist to the North West Coast of Tasmania, etc. 212 pages; 24 × 15.5 cm. 1960. Medical Book Department, Little, Brown & Company, Boston. Price, \$6.50.
- Modern Scientific Aspects of Neurology. Edited by John N. Cumings, M.D., F.R.C.P., Professor of Chemical Pathology, Institute of Neurology, The National Hospital, Queen Square, London. 360 pages; 23.5 × 15.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$13.00.
- Population Characteristics and Participation in the Poliomyelitis Vaccination Program. Public Health Monograph No. 61; Public Health Service Publication No. 723. 37 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.
- P-Q-R-S-T: A Guide to Electrocardiogram Interpretation. 4th Ed. By Joseph E. F. RISEMAN, M. D., Assistant Clinical Professor of Medicine, Harvard Medical School, etc. 168 pages; 15.5 × 21.5 cm. 1960. The Macmillan Company, New York. Price, \$6.50.
- Practical Clinical Management of Electrolyte Disorders. By WILLIAM J. GRACE, Director of Medicine, The St. Vincent's Hospital of the City of New York, etc. 144 pages; 21 × 14 cm. 1960. Appleton-Century-Crofts, Inc., New York. Price, \$4.95.
- The Principles and Practice of Medicine: A Textbook for Students and Doctors. 5th Ed. By Sir Stanley Davidson, B.A. Cantab., M.D., F.R.C.P. Edin., F.R.C.P. Lond., M.D. Oslo, F.R.S. Edin., Physician to H. M. the Queen in Scotland, etc.; and Past and Present Members of the Staff of the Department of Medicine, University of Edinburgh, and Associated Clinical Units. 1,112 pages; 22.5 × 14.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$8.00.
- Radiation: Use and Control in Industrial Application. Modern Monographs in Industrial Medicine, 5. (Editor in Chief: Anthony J. Lanza, M.D.; Consulting Editor: Richard H. Orr, M.D.) By Charles Wesley Shilling, M.D., Sc.D., Deputy Director, Division of Biology and Medicine, United States Atomic Energy Commission, Washington, D. C. 223 pages; 22.5 × 14.5 cm. 1960. Grune & Stratton, New York. Price, \$6.75.

#### MEDICAL NEWS

POSTGRADUATE EDUCATION

The following Postgraduate Courses, under the auspices of the American College of Physicians, have been planned for Fall-Winter, 1960-61:

November 7–11, 1960	ELECTROCARDIOGRAPHY, Dr. Hans H. Hecht, Director,
	University of Utah College of Medicine, Salt Lake City, Utah.
December, 1960	RECENT ADVANCES IN PHARMACOTHERAPY, Dr. Robert
(date not set)	H. Williams, Director, University of Washington School of Medicine, Seattle, Wash.
January 16-20, 1961	GENERAL MEDICINE, Dr. Stanley E. Bradley, Director, Columbia-Presbyterian Medical Center, New York, N. Y.
February 20-24, 1961	SELECTED TOPICS IN INTERNAL MEDICINE, Dr. Stewart Wolfe, Director, University of Oklahoma Medical Center, Oklahoma City, Okla.

For registration blanks and other information, contact Dr. Edward C. Rosenow, Jr., Executive Director, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

A three-day symposium, "Surgery of Endocrine Organs," will be presented by the schools of medicine of the New York University Medical Center November 17 to 19, 1960.

Surgical diseases in which the endocrine system is directly involved or in which endocrine influences are important will be discussed. Functioning tumors of endocrine structures, derangements of internal secretions that are amenable to surgical treatment, and endocrine factors in metastases of cancer are considered from physiologic and diagnostic standpoints.

A round table discussion by all the participants Saturday morning (November 19) concludes the symposium.

Further details, including an application, may be obtained from the Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, New York.

- Nov. 9–18

  Postgraduate Seminar Cruise to the Virgin Islands and Puerto Rico, sponsored by Duke University Medical School. Lectures on thyroid abnormalities, chemical treatment of cancer, arthritis, diabetes, and blood disease. For information contact Director of Postgraduate Education, Duke University Medical Center, Durham, N. C.
- Dec. 5-9

  Symposium on Inflammation and Diseases of Connective Tissue: Pathogenesis and Therapy. This symposium, to be held under the auspices of Hahnemann Medical College, will consist of a five day morning and afternoon program of lectures and panel discussions. Further details may be obtained from Dr. Lewis C. Mills, Hahnemann Medical College, 230 Broad Street, Philadelphia 2, Pennsylvania.

#### POSTGRADUATE COURSES FOR INDUSTRIAL PHYSICIANS

#### February 3-7, 1961

The Columbia University School of Public Health and Administrative Medicine Program of Continuation Education announces its Fourth Annual Institute for Physicians in Industry to be held February 3–7, 1961, in New York City.

For further information, inquiries may be directed to:

Program of Continuation Education School of Public Health and Administrative Medicine 600 West 168th St. New York 32, N. Y.

#### FELLOWSHIPS

The Arthritis and Rheumatism Foundation offers predoctoral, postdoctoral and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning on July 1, 1961. The deadline for applications is October 31, 1960.

Further information may be obtained from the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N. Y.

Lemuel Shattuck Hospital, in coöperation with Warren Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at Massachusetts General Hospital, has established a chemotherapy fellowship. The program will provide training in the use and critical evaluation of new chemotherapeutic agents in man and animals. There will be opportunity for individual research. Fellows should have prior training in internal medicine. For information contact Oncology Division, Medical Services, Lemuel Shattuck Hospital, Boston 30, Mass.

The Department of Pediatrics, New York University-Bellevue Medical Center, College of Medicine, has announced a fellowship available in pediatric allergy. The fellow will participate in current research activities and attend clinical sessions at Bellevue and University Hospitals. Applicants should have a minimum of two years in pediatrics. Salary will be \$4,500 to \$5,000. For information contact Vincent J. Fontana, M.D., NYU-Bellevue Medical Center, 550 First Avenue, New York 16, N. Y.

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1961, as follows: (1) Until October 15, 1960, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend \$4,500, with allowances for dependents and necessary travel. (2) Until November 1, 1960, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17. N. Y.

The Memorial Center for Cancer and Allied Diseases of Cornell University Medical College offers special fellowship for study in medical neoplasia. Candidates must be graduates of A.M.A. approved medical schools and must have completed or be in the process of completing two years of postgraduate training in internal medicine in addition to one year of internship. The salary stipend is \$6,000 per year without maintenance. It is for one year, renewable for two. For information contact Dr. Henry D. Diamond, Chief, Lymphoma Service, Department of Medicine, Memorial Center of Cancer and Allied Diseases, 444 E. 68th St., New York 21, N. Y.

The Scientific Advisory Committee of the Licensed Beverage Industries, Inc., has announced a new grant-in-aid program for scientists working in the field of alcoholism and related subjects. Grants will be awarded to qualified scientists in the biological and behavioral sciences who wish to make pilot studies for the purpose of raising or clarifying promising hypotheses. Stipends will range from \$2,000 to \$10,000 and may be renewed. Recipients will have complete freedom of operation. For information contact the above Committee, 155 E. 44th St., New York City 17, N. Y.

#### FUTURE MEETINGS

Oct. 31-Nov. 4, 1960	American Public Health Association, San Francisco.
	Contact: Berwyn F. Mattison, M.D., Exec. Dir., 1790
	Broadway, New York 19.
Nov. 1-2	Association of Military Surgeons of the U.S. at Wash-
	ington, D. C. Headquarters: Mayflower Hotel. General
	Chairman: Rear Adm. Curtiss W. Schantz, DC, U. S.
	Navy, Asst. Chief of Bureau of Medicine & Surgery for
	Dentistry, Navy Department, Washington 25, D. C.
Nov. 2-5	American Society of Tropical Medicine and Hygiene.
	Biltmore Hotel, Los Angeles. Contact: Rolla B. Hill,
	M.D., Executive Secretary, 3575 St. Gaudens Rd., Miami
	33, Florida.
Nov. 8-10	Medical Society of the United States and Mexico at
	Guadalajara, Jalisco, Mexico. This will be followed by
	a two day session in Mazatlan, Sinaloa, Mexico on Nov.
	11-12. For information, contact M. A. Carreras, M.D.,
	Secretary, 130 South Scott, Tucson, Arizona.
Nov. 26-28	American College of Chest Physicians at Washington,
	D. C.
Nov. 28-Dec. 2, 1960	American Medical Association, Clinical Meeting, Wash-
	ington, D. C. F. J. L. Blasingame, 535 N. Dearborn,
	Chicago 10, Ill.
Nov. 30-Dec. 3, 1960	Canadian Heart Association and National Heart Founda-
,	tion of Canada, Toronto. J. B. Armstrong, 501 Yonge
	St., Toronto 5, Canada.
Mar. 13-16, 1961	National Health Council, National Health Forum at New
	York City, N. Y. Hdqts: Waldorf-Astoria. For infor-
	mation contact Mr. Philip E. Ryan, 1790 Broadway, New
	York 19, N. Y., Executive Dir.

Apr. 21-23, 1961 American Society for the Study of Sterility at Bal Harbour, Miami Beach, Fla. Hdgts: The Americana. Dr. Herbert H. Thomas, 920 S. 19th St., Birmingham 5, Ala., Sec'y. Apr. 29-30, 1961 The American Psychosomatic Society will hold its annual meeting at the Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey. The deadline for submission of abstracts is December 1, 1960. Abstracts should be addressed to The Chairman, Program Committee, 265 Nassau Road, Roosevelt, N. Y. Sept. 3-10, 1961 Inter-American Congress of Radiology at Sao Paulo, Brazil. Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil, Sec'y-Gen. Sept. 6-12, 1961 International Congress on Human Genetics at Rome, Italy. Prof. Luigi Gedda, 5 Piazza Galeno, Italy. Nov. 16-18, 1961 International Symposium on the Etiology of Myocardial Infarction at Detroit, Mich. Hdqts: Henry Ford Hospital. Dr. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich., Chairman, Section on Cardiovascular Research.

#### TERATOLOGY SOCIETY

For several years scientists interested in basic problems of congenital malformations have held informal conferences in which questions of common interest were discussed. Anatomists, biochemists, embryologists, geneticists, obstetricians, pathologists, pediatricians, plastic surgeons and others attended these conferences which were in part supported by the Association for the Aid of Crippled Children, New York, N. Y., and the Human Embryology and Development Study Section of the National Institutes of Health. Following the fourth teratology conference, which was held at the Memorial Sloan-Kettering Cancer Center in New York City and attended by 76 scientists from Canada, England, France, Germany and the U. S. A., "The Teratology Society" was formed. The following officers were elected: President: Josef Warkany, M.D., Cincinnati, O.; President-Elect: James G. Wilson, Ph.D., Gainesville, Fla.; Secretary-Treasurer: Marjorie M. Nelson, Ph.D., San Francisco, Calif.; Recorder: Sidney Q. Cohlan, M.D., New York, N. Y.; Council: F. Clarke Fraser, Ph.D., M.D., Montreal, Canada, David L. Gunberg, Ph.D., Portland, Ore., and M. Lois Murphy, M.D., New York, N. Y. The National Foundation assisted in the formation of the Society with advice and financial aid. Inquiries about The Teratology Society should be directed to Dr. Marjorie M. Nelson, Department of Anatomy, School of Medicine, University of California, San Francisco 22, Calif.

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1. Eisen, H. N., and Tabachnick, M.: Protein Metabolism, M. Clin, North America 39:863 (May) 1955. 2. Jamison, R. M.: General Nutritive Deficiency, Virginia M. Month. 83:67 (Feb.) 1956. 3. Goldfarb, A. F.; Napp, E. E., Stone, M. L.; Zuckerman, M. B., and Simon, J.: The Anabolic Effects of Norethandrolone, a 19-Nortestosterone Derivative, Obst. & Gynec. 11:454 (April) 1958. 4. Batson, R.: Investigator's Report, Feb. 11, 1956. 5. Weston, R. E.; Isaacs, M. C.; Rosenblum, R.; Gibbons, D. M., and Grosman, J.: Metabolic Effects of an Anabolic Steroid, 17-Alpha-Ethyl-17-Hydroxy-Norandrostenone, in Human Subjects, J. Clin Invest. 35:744 (June) 1956. 6. Brown, C. H.: The Treatment of Acute and Chronic Ulcerative Colitis, Am. Pract. & Digest Treat. 9:405 (March) 1958.

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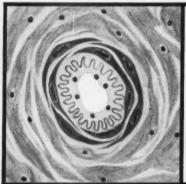
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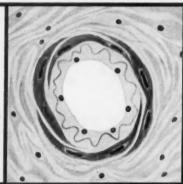
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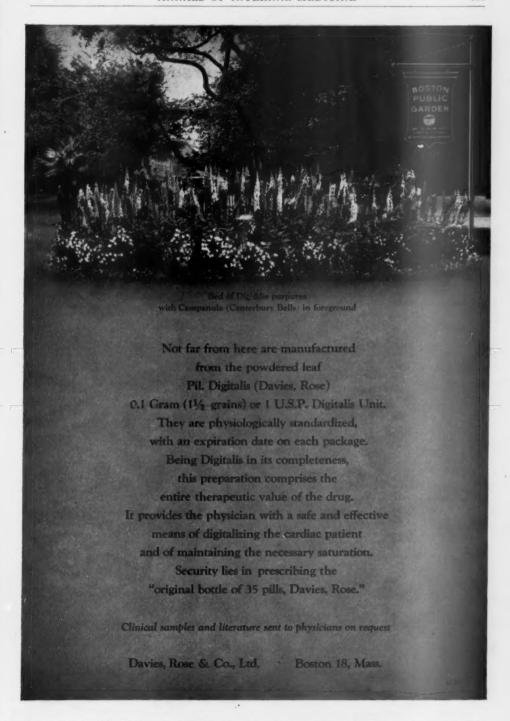
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orien in der Chirurgie, Med. Klin. 49:1921-22, 1954. 53. Millack, J.: Obstipationstherapie wachrend der Graviditaet 'raxis 9/6: (Feb.) 1957. 54. Moreton, R. D.: The roentagenologic of thination of the colon, presented at the Annua of the American Roentgen Ray Soc., Wash., D.C., Oct. 1, 1433. 55. Ohling, A. C.: Rektale Anwendung von Laxantien ische 22:819-821, 1955. 56. Pincock, J. G.: The use of a rectal surposition of bisacodyl (Dulcolax) in geriatric patients M.A.J., 82:268-269 (Jan. 30) 1960. 57. Poppel, M. H.: Bowel presitation for radiologic procedures using a new evacuant J. Am. J. Roentgenol. 81:696-699 (Apr.) 196. 98. Raykim, H. F. Palmyr, W. L., and Kirsner, J. B.: Exblistive cytology osis of cancer of the allow. Dis. Colon & Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 959. 59. Raymond, O.: Nogrady, B. and Vezina (Restume 2:655. [In.-Feb. 95 of bisacodyl (Dulcolax) in gertatric patients for radiologic procedures using a new evacuant W. L., and Kirsner, J. B.: Exfoliative cytolog: 1, 59, Raymond, O.; Nogrady, B. pnd Vezina diology, Scien. Exhibit presented at the 22nd of the Company o iffective evacuation of Meeting of the Canad Meeting of the Canadina ) 1960. 61. Roth, F.: Dulcolax in K 1958. 62. Rutter, A. G.: Bisacodyl; chez Martin, Agustin: Estermentac. Schaal, W., und Bachin, W.: Erf Med. klin, 48,1072-73, 193. 65. einem neued Kontakt Laxins, Med. ia) 36:372-376 (Nov.)

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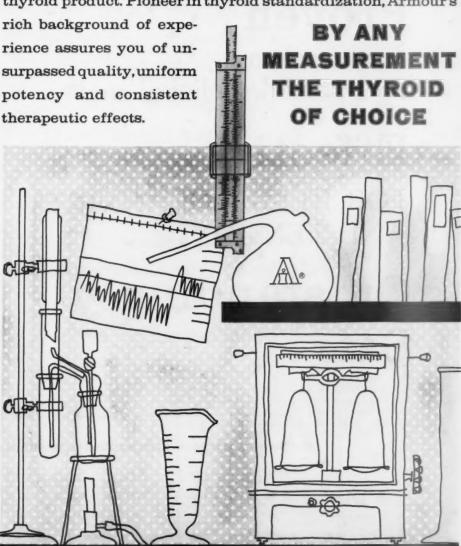
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1. Blumberg, N. et al.: Fed. Proc. 17:351, March 1958. 2. Boyd, L. J. et al.: Am. J. Cardiol. 3:229, Feb. 1959. 3. Brick, H. et al.: J. Social Therapy 4:190, 1958. 4. Bulla, J. D. et al.: Am. Proct. 8. Digest Treat. 10.1961, Nov. 1959. 5. Ewing, J. A. and Halzlip, T. M.: Am. J. Psychiat. 114:835, March 1958.

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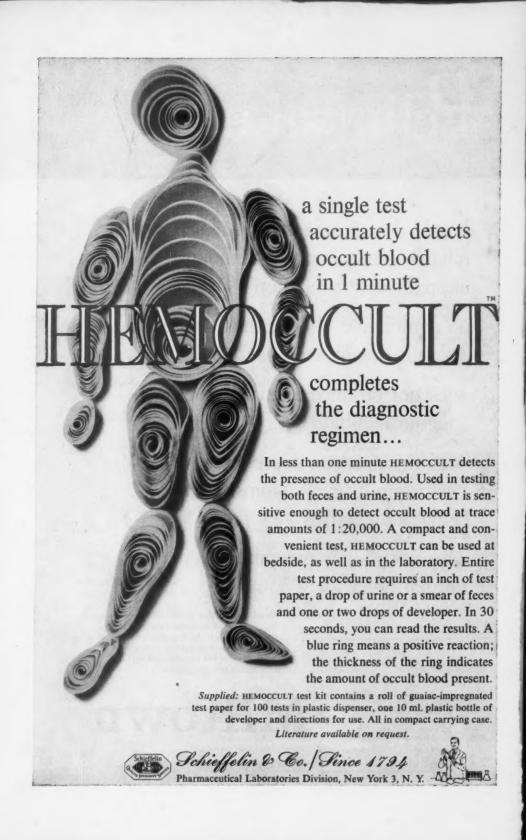
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#### IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



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... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

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Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

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#### REFERENCES

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# Schedule of Postgraduate Courses, Autumn-Winter, 1960-1961 THE AMERICAN COLLEGE OF PHYSICIANS

	Sept.			Oct.	-	.	4	Nov.			Dec.	3	T	-		Jan.	-	T	1	Feb.
These courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees: Members, \$60.00; Non-members, \$60.00; Full details may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.	19-23	7-5	10-14	17-21	24-28 Oct, 31-Nov, 4	7-11	81-18	21-25	Nov. 28-Dec. 2	6-5	12-16	19-23	26–30	9-7	61-6	12-50	73-27	Jan. 30-Feb. 3	01-6	13-27
Course No. 1, THE PLACE OF HEMATOLOGY IN INTERNAL MEDICINE: WITH AN INTERODUCTION TO RADIOISOTOPE TECHNICS AND THEIR APPLICATION: The Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director.	×						1													
Course No. 2, CANCER AND THE INTERNIST—1960 CONCEPTS: Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N. Y.; Rulon W. Rawnon, M.D., F.A.C.P., Director		1	×			1	1						Ī	1	1	1		İ	1	
Course No. 3, THE PHYSIOLOGIC BASIS OF ELECTROCARDIOGRAPHY: University of Utah College of Medicine, Salt Lake City, Utah; Hans H. Hecht, M.D., F.A.C.P., Director.		1			1	×	lu lu			1			Ī		1	1		Ī	1	
Course No. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.						1									×				-	
Course No. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., Co-Directors.				1		<u> </u>	1									×				
Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahama School of Medicine and University Hospitals. Oklahama City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammartten, M.D., F.A.C.P., C-Drectors, M.D., Associate), Associate Director.	1					1	1					1	Ì					İ		

The following courses are scheduled for Spring, 1961: CARDIOVASCULAR DISEASES, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6-10; INTERNAL MEDICINES. SEECTED TOPICS. McGill University, vi H. Philip Hill, M.D., F.A.C.P., Director, March 13-17; ADDVANCED CLINICAL ELECTRECARDIOGEARPHY, The University of Tennessee, I. Frank Thilis, M.D. F.A.C.P., Director, March 20-24; ENDOCRINOLOGY AND METABOLISM, University of Virginia William Parson, M.D., F.A.C.P., Director, March 23-45; PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, May 15-19; CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19-23.

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#### CLINICAL EVALUATION OF 486 EPILEPTIC PATIENTS" SHOWED THAT:

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\*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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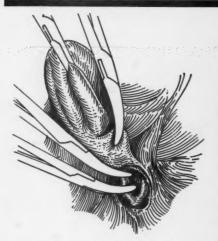


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Source: Farris, J. M., and Smith, G. K.: M. Clin. North America 43:1133 (July) 1959. when the patient needs increased bile flow...

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"Constant loss of bile [from relaxation of sphincter of Oddi following cholecystectomy] reduces the amounts available for lipid absorption after meals, with resulting clinical symptoms apparently relieved by bile acid administration." *Source:* Popper, H., and Schaffner, E.: Liver: Structure and Function, New York, McGraw-Hill, 1957, p. 309

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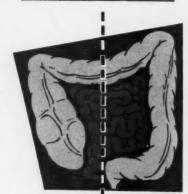
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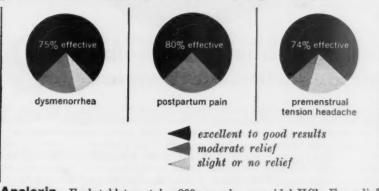
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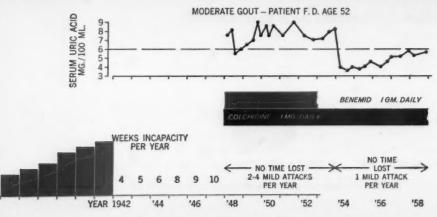
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1. Talbott, J. H.: Gout, New York, Grune &

Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.:

Gouty arthritis, Minn. Med. 48:1044, Aug.

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**ROMILAR** is of special value when cough suppression is vital—in patients with pulmonary and cardiac disease, hernia or rib fracture, before and after abdominal and EENT surgery and during i.v. infusions.

SUPPLY: Syrup in bottles of 4 oz, 16 oz, 1 gal. Tablets in bottles of 20, 100, 500. Expectorant in bottles of 16 oz, 1 gal.

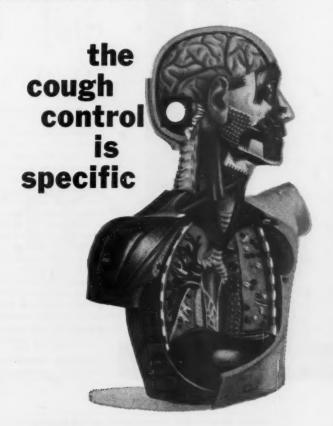
REFERENCES: 1. H. A. Bickerman in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. 2. L. J. Cass and W. S. Frederik, New England J. Med., 249:132, 1953. 3. L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc., 227:291, 1954. 4. H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap., 107:524, 1953. 5. W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap., 109:189, 1953. 6. New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, 1959, p. 326. 7. N. Ralph, Am. J. M. Sc., 227:297, 1954. 8. H. A. Bickerman, E. German, B. M. Cohen and S. E. Itkin, Am. J. M. Sc., 234:191, 1957.

Romilar

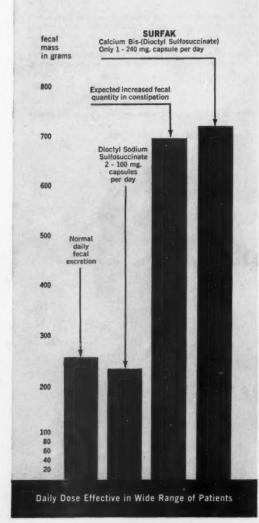
NON-NARCOTIC COUGH SPECIFIC WITH PROMPT, PROLONGED ACTION



ROCHE LABORATORIES . Division of Hoffmann-La Roche Inc . Nutley 10, N. J.



# Comparative Effectiveness in softening fecal mass



# ONE

# **SURFAK**

# Capsule softens up to 3 times the normal daily fecal excretion

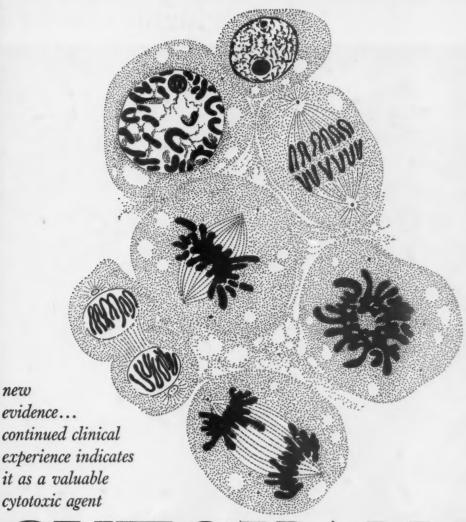
Therapeutic effectiveness in constipation depends on a more complete softening of the increased fecal load. ONE Surfak capsule is all that is needed to soften fecal matter up to three times the normal daily fecal excretion. This superior fecal softening effectiveness of Surfak is demonstrated in the chart shown, which indicates that a much wider range of patients—even those with severe constipation—can be successfully treated with only one capsule daily with usually complete freedom from side effects. Surfak is non-laxative, thus eliminating the "griping," flatulence, oily leakage or danger of habituation often associated with laxative therapy.

DOSAGE: One Surfak 240 mg. soft gelatin capsule daily for adults. Surfak 50 mg. soft gelatin capsules—for children, and adults with minimum needs, one to three daily.

SUPPLY: 240 mg.-bottles of 15 and 100. 50 mg.-bottles of 30 and 100.

LLOYD BROTHERS, INC.

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# CYTOXA Johnson

#### FOR PALLIATIVE CHEMOTHERAPY OF CERTAIN TYPES OF MALIGNANT NEOPLASMS

Report from a recent comparative clinical evaluation of two alkylating agents: "With the use of cyclophosphamide [Cytoxan], there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."\*

Other Advantages in Clinical Practice: Broad spectrum of application • High therapeutic index • No vesicant activity—may be given orally or parenterally.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department (Section B), Mead Johnson & Company, Evansville 21, Indiana.

Papac, R.; Petrakis, N. L.; Amini, F., and Wood, D. A.: J.A.M.A. 172:1387-1391 (March 26) 1960.



highly effective,

in allergic and inflammatory skin disorders, including psoriasis

unsurpassed for total corticosteroid benefits

Substantiated by published reports of leading clinicians:

• effective control of inflammatory and allergic symptoms



• biochemical and psychic balance disturbance minimal 1,4-18 well-tolerated control

# Triamcinolone LEDERLI

## A Promise Fulfilled

All corticosteroids provide symptomatic control in rheumatoid arthritis, bronchial asthma and inflammatory dermatoses. They differ in the frequency and severity of side effects. Introduced in 1958, Aristocort Triamcinolone bore the promise of high efficacy and relative safety.

Physicians today recognize that the promise has been fulfilled ... as evidenced by the high rate of refilled ARISTOCORT prescriptions. List of References 1-18 supplied on request.

Precautions: With ARISTOCORT all precautions traditional to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms.

#### Supplied:

1 mg. scored tablets (yellow)

2 mg. scored tablets (pink)

4 mg. scored tablets (white)

16 mg. scored tablets (white)



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

on Modutrol PEPTIC ULCER SYMPTOMS DO NOT REAPPEAR after-hours... after stress... after years!

Modutrol allows complete and lasting freedom from symptoms - without dietary restrictions. Of all agents tested, only Modutrol achieved the three rigid objectives for success in peptic ulcer therapy: relief of symptoms, healing of ulcer and prevention of recurrences or complications. Moreover, Modutrol met these criteria in over 96 per cent of all patients tested.1

Psychophysiologic Medication To Combat A "Psychovisceral Process"

Therapeutic efficacy of Modutrol is enhanced by its psycho-active component, Sycotrol-proved clinically to be not only more effective than either sedatives or tranquilizers, but ideally suited for ambulatory patients because they do not experience commonly encountered side effects of depression and habituation. Sycotrol, a psychotropic agent with antiphobic properties, acts against fears and anxieties that find outlets in visceral manifestations. Modutrol combines the psycho-active agent with preferred antacid and anticholinergic therapy to provide total management of the disorder.

FORMULA: Each Modutrol tablet contains; Sycotrol (pipethanate hydrochloride) 2 mg., scopolamine methylnitrate 1 mg., magnesium hydroxide 200 mg., aluminum hydroxide 200 mg.

DOSAGE: One tablet 3 or 4 times daily.

SUPPLIED: Bottles of 50 and 100 tablets,

CONTRAINDICATIONS: Contraindicated in glaucoma because of its anticholinergic components.

1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

Also available: Sycotrol tablets 3 mg. Bottles of 100 tablets.

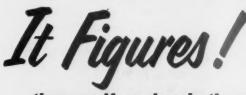


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Psycho-physiologic Management



When the Target Organ of Fear-anxieties is the G.I. Tract and Peptic Ulcer Results.



the self-calculating L-F BASALMETER® gives BMR test results quickly, easily, more reliably

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First, set the four basic factors.







After machine has completed its cycle, a touch of a button gives the BM rate on the easy-toread meter.





Say goodbye to the charts, graphs, slide rules-the tedious, sometimes inaccurate computations—usually

associated with basal metabolism testing.

How? By putting a BasalMeteR to work in your practice. This is the swift, sure, modern way to do BMR testing. Human error is eliminated; the BasalMeteR does all the calculating.

Install a BasalMeteR in your office now. It eliminates referrals, gives you BMR results immediately and broadens the scope of your services to your patients. Your patients will also appreciate your concern for their convenience.

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Please send me more information on the BasalMeteR.

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# CONSISTENTLY GOOD CLINICAL RESULTS IN TRICHOMONAL AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder) cured 143 of 161 patients with vaginitis due to Trichomonas vaginalis, Candida (Monilia) albicans, or both. "Almost immediate symptomatic improvement was noted with the first insufflation."

Criteria for cure: freedom from infecting organisms as well as symptoms on repeated examinations during a three-month follow-up. This cure rate of 88.8% is "surprisingly similar" to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.: J.M.A. Georgia 48:167, 1959.

# TRICOFURON°

**IMPROVED** 

2-step treatment brings swift relief, eradicates stubborn trichomonads, Candida (Monilia) albicans, Hemophilus vaginalis

1. POWDER for weekly insufflation in your office.

MICOFUR®, brand of nifuroxime, 0.5%
and FUROXONE®, brand of furazolidone, 0.1% in
an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use

—1st week one suppository in the morning
and one on retiring. After 1st week, one
suppository at night may suffice.

Continue use of suppositories during menses.

Treatment should be continued throughout a complete menstrual cycle and for several days thereafter.

Micofur 0.375% and Furoxone 0.25% in a water-miscible base.

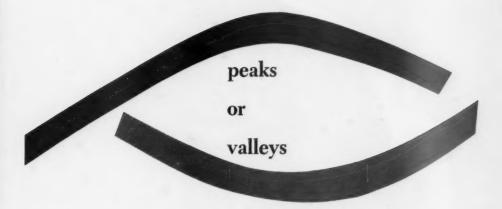
Rx new box of 24 suppositories with applicator for more practical and economical therapy.

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NITROFURANS—a unique class of antimicrobials EATON LABORATORIES, NORWICH, NEW YORK

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# DIGITALINE

the original crystalline digitoxin

# NATIVELLE

You will find that Digitaline Nativelle, the original crystalline digitoxin, provides exactly the balanced, controlled maintenance dose you want for your cardiac patient. Its duration of activity is neither too short nor unduly prolonged, well suited to daily maintenance therapy. Its complete absorption and purity assure uniform potency, precision of dosage, total utilization and effectiveness. A product of Nativelle, Inc.

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E. Fougera & Company, Inc., Hicksville, Long Island, N. Y.

after initial digitalization...

a lifetime of balanced

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# gentle relaxant-sedative

WITH TIMED-RELEASE ACTION FOR A FULL NIGHT'S SLEEP

# nebralin

TIMED-RELEASE TABLET

Might as well try to put a tiger to bed (and keep him there) as to get most patients to sleep naturally all night. For disturbed, interrupted sleep is the most common sleep problem in routine practice. Nebralin—a timed-release tablet—encourages muscular relaxation and sustained, relaxed sleep. The combination of mephenesin and Dorsital\* in Nebralin not only relaxes skeletal muscles, overcomes "fatigue-tension" and conditions the body for sleep, but also induces sound, relaxed sleep by gentle CNS sedation. Mephenesin is capable of producing sleep, and when combined with a barbiturate enhances barbiturate action. Moreover, the integrated action of the two components permits smaller dosage of each. Thus, Nebralin—a gentle relaxant-sedative—avoids morning hangover, and carries your patients through the middle of the night, especially those patients who complain about waking up at 2 A.M.

Schlesinger, E. B.: Tr. New York Acad. Sc. 2:6 (Nov.) 1948.
 R. K., and Taylor, J. D.: Anesthesiology 17:414, 1956.
 Shideman, F. E.: Postgrad. Med. 24:207, 1958.
 Berger, F.: Pharmacol. Rev. 1:243, 1949.



Each Nebralin timed-release tablet contains: Dorsital\*, 90 mg.; Mephenesin, 425 mg. Dosage: One or two tablets ½ hour before retiring. Supplied: Bottles of 50 Nebralin timed-release Tablets.

\*Dorsey brand of pentobarbital.

# ONLY QUINAGLUTE' DURA-TAB S.M.

PROVIDES ORAL QUINIDINE

GLUCONATE (5 gr.)

...BETTER
TOLERATED

because it is 10 times as soluble as the sulfate

SAMPLES and literature — write.



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CORPORATION
Lancaster Ave. at 51st St.
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in q. 12 h. dosage each Sustained Medication\* dose maintains uniformly effective, virtually non-fluctuating blood levels, all day, all night.

in cardiac arrhythmias for maximum quinidine efficacy, tolerance, convenience<sup>1-5</sup>— specify Quinaglute Dura-Tab S.M. Bottles of 30, 100 and 250.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960.

\*U.S. Patent 2,895,881

Hard filled capsules in bottles of 30.

4 mg.

# Medrol Medules

pH-patterned slow release...

not here at pH 1.2

In the relatively acid medium of the fasting stomach, Medules are kept essentially intact by their special pH-sensitive coating (about 5% of Medrol content released in 2 hours at pH 1.2).

but here at pH 7.5

In the environment of the duodenum (at pH of approximately 7.5) 90% to 100% of the Medrol content is released within 4 hours.

...means gradual steroid absorption



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**TOLERATED** 

because it is 10 times as soluble as the sulfate

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in q. 12 h. dosage each Sustained Medication\* dose maintains uniformly effective, virtually non-fluctuating blood levels, all day, all night.

in cardiac arrhythmias for maximum quinidine efficacy, tolerance, convenience1-5 - specify Quinaglute Dura-Tab S.M. Bottles of 30, 100 and 250.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960. also available: INJECTABLE QUINAGLUTE

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4 mg.

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pH-patterned slow release...

not here at pH 1.2

In the relatively acid medium of the fasting stomach, Medules are kept essentially intact by their special pH-sensitive coating (about 5% of Medrol content released in 2 hours at pH 1.2).

but here at pH 7.5

In the environment of the duodenum (at pH of approximately 7.5) 90% to 100% of the Medrol content is released within 4 hours.

...means gradual steroid absorption

135 tiny doses mean  ${
m smoother}^{**}$ steroid therapy (\*\*So smooth and protracted that even among rheumatoid arthritis patients "morning stiffness

Upjohn

tracted that even among rheumatoid arthritis patients 'morning stiffness in a great majority of these patients just doesn't exist any more. They wake up comfortable.' Iuppa, N. V. Curr. Therap. Res. 2:177 (June) 1960.

Medrol hits the disease, but spares the patient

\*Irademark, Reg. U.S. Pat. Off.methylprednisolone, Upjohn

# PRURITUS ANI Treated Orally with

Borcherdt's MALT SOUP EXTRACT (MALTSUPEX) @ POWDER LIQUID

#### shows good results

Acts by promoting aciduric flora in the colon. Stools and secretions become slightly acid rather than strongly alkaline. Itching and burning usually relieved in 3 days.(1)

Consists of non-diastatic barley malt extract neutralized with 1.5% potassium carbonate. Non-habit forming. Safe for long-term use if needed. Diabetic should allow for carbohydrate content. See P.D.R.

Usual dose 2 Tbs. twice a day. Available, liquid and powder, 8 and 16 oz. bottles at pharmacies.

#### Send for clinical samples

(1) Brooks, L. H.: Dis. of Colon & Rectum, v. 1, no. 5, 1958

# Borcherdt Company 217 North Wolcott Avenue, Chicago 12, Illinois.

## **FUTURE ANNUAL** SESSIONS

1961-Miami Beach, Fla., May 8-12

1962—Philadelphia, Pa., April 9-13

1963—Denver, Colorado, April 1-5

1964-Atlantic City, New Jersey, April 6-10

## ARE YOU MOVING?

PLEASE NOTIFY US OF ANY CHANGE OF ADDRESS AND FORWARD TO:

> ANNALS OF INTERNAL MEDICINE. 4200 Pine St., Philadelphia 4, Pa.

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OLD ADDRESS:	NEW ADDRESS:
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REMARKS	

THE SULPA COMPOSITE THAT IS A SULPAGIALLY IN THE SULPAGIALLY IN THE SULPAGIAL OF THE SULPAG

"Thiosulfil" Forte

See over for therapy in difficult patients >

HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

#### PROOF OF EFFECTIVENESS

In acutely infected patients: Results of seven years' clinical experience: Bourque's report covers 3,057 patients treated with "Thiosulfil" for upper and lower urinary tract infections. The causative organisms were E. Coli, Pseudomonas, Klebsiella, Enterococcus, Staphylococcus, Alcaligenes fecalis, and Proteus.

The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:<sup>2</sup> "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections: "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . . "

"'Thiosulfil" was ineffective in only 7 per cent . . ." dosage: 2 Gm./day

## RECORD OF SAFETY

The Sulfa Compound Used Successfully Without Interruption for: one month; <sup>3,4</sup> more than 6 weeks; <sup>2</sup> 90 days; <sup>5</sup> 18 months; <sup>3</sup> 5 to 6 years. <sup>7</sup>

## **DOSAGE** (Urinary Tract Infections)

TIME PERIOD	DOSE	
First two weeks	First two weeks 3 Gm./day1	
2 weeks to 3 months	2 Gm./day <sup>3,4</sup>	
3 months or longer	0.5 Gm./day <sup>7</sup>	

<u>Suggested Range of Dosage</u>: 1 or 2 tablets three or four times daily. <u>Note</u>: The usual precautions exercised with sulfonamides should be observed. <u>Supplied</u>: No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

References—1. Bourque, J.P., and Gauthier, G.E.: Seven years' experience with sulfamethizole, to be published. 2. Barnes, R. W.: J. Urol. 71:655 (May) 1954. 3. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 4. Bourque, J-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 5. Hughes, J., Coppridge, W. M., and Roberts, L. C.: South. M. J. 47:1082 (Nov.) 1954. 6. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VAL-UABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUP-TION—FOR WEEKS, MONTHS...EVEN YEARS.

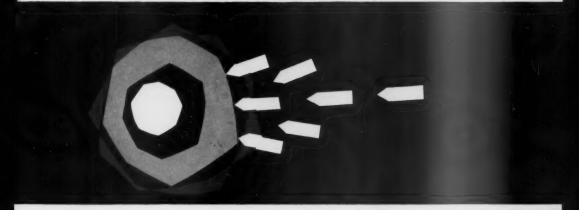
# "Thiosulfil" Forte

AYERST LABORATORIES, NEW YORK 16, N.Y., MONTREAL, CANADA

to meet the allergic attack...with b.i.d. dosage

# TREBUIS AND THE PROBLEM OF THE PROBL

inherently sustained action at the cellular level



#### inherently sustained action

Tacaryl possesses inherent long-acting properties. After rapid disappearance from the blood stream, Tacaryl is bound to the tissues. This protective affinity for tissue provides a notably sustained effect which does not depend upon the use of artificial, long-acting construction. The sustained action, an inherent property of the molecule, lasts for periods up to 12 hours.

#### rapid absorption-rapid relief

Tacaryl is absorbed quickly to provide relief of symptoms within an hour.

#### low toxicity-minimal side effects

In studies to date, side effects were minimal; in a small percentage of patients, mild drowsiness was observed. Tolerance was not reported even after long usage. No cumulative effect has been observed.

#### clinically proved

In studies of 459 patients, 1 Tacaryl provided effective symptomatic relief in a wide variety of con-

ditions, including allergic rhinitis, pruritus, various skin disorders, allergic bronchial asthma, pruritus of chickenpox, and allergic conjunctivitis. In some cases, the relief of itching bordered on the dramatic.<sup>2</sup> In a double-blind clinical evaluation<sup>3</sup> of various antihistaminic agents in hay fever, Tacaryl provided benefits in all patients with moderate to severe symptoms.

**desage:** adults—One tablet (8 mg.) or two 5 cc. teaspoonfuls syrup (8 mg.) twice daily. children—One-half tablet (4 mg.) or one 5 cc. teaspoonful syrup (4 mg.) twice daily.

In some cases it may be desirable to adjust dosage to meet individual requirements.

supply: Scored tablets, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. teaspoonful, 16 oz. bottles.

references: (1) Clinical Research Division, Mead Johnson & Company. (2) Howell, C. M., Jr.: Evaluation of Methdilazine Hydrochloride as an Antipruritic Agent, North Carolina M. J. 21 (May) 1960 (in press). (3) Wahner, H. W., and Peters, C. A.: An Evaluation of Some Newer Antihistaminic Drugs Against Pollinosis, Proc. Staff Meet. Mayo Clin. 35:161-169 (March 30) 1960.



17760

# ISMELIN® reduces high blood pressure to

According to reports from more than 100 clinical investigators, Ismelin-in moderate to severe hypertension-reduces blood pressure levels to normal or near-normal in a remarkably high percentage of patients. Following are summaries of typical findings:

17 of 18 patients (94.4%) treated with Ismelin become normotensive in the erect position. Page and Dustan1 gave Ismelin orally, alone or in combination with other antihypertensive drugs, to 18 patients daily for 2 to 10 weeks.

RESULTS: All 18 patients had reductions in standing blood pressure; 16 had moderate reductions in supine blood pressure as well. In 17 of the 18 cases, blood pressure levels became normal or near-normal in the erect position.

	TOLIC	anding B.P.	
173 mm. Hg	AFTER ISMELIN®  131 mm. Hg	115 mm. Hg	AFTER ISMELIN

\*During last week of treatment.

In 14 of 15 patients (93.3%) on Ismelin, blood pressure reduced to normal or near-normal levels in the standing position. Ismelin was administered orally by Frohlich and Freis2 for 4 to 9 weeks to 15 male patients selected from the hypertensive clinic.

Average S	tanding B.P.	
SYSTOLIC	DIASTOLIC	
181 AFTER ISMELIN Hg 132 mm. Hg	CONTROL  AFTER ISMELIN Hg 90 mm Hg	

RESULTS: Ismelin evoked a potent antihypertensive response in the erect position: the blood pressure of 14 of the 15 patients dropped to normotensive or near-normotensive levels.

"The response [to Ismelin] was

characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade."2

In 15 of 18 subjects (83.3%), guanethidine [Ismelin] reduced high blood pressure to near-normotensive levels. Guanethidine [Ismelin] was administered orally by Richardson and Wyso3 to 18 male hospitalized patients with hypertension.

Av	erage St	anding B	.P.
SYS	TOLIC	DIASTOLIC	
195 mm. Hg	AFTER ISMELIN 139 mm. Hg	129 mm. Hg	AFTER ISMELIN

References: I. Page, I. M., and Dustan, H. P.: J.A.M.A. 170:1265 (July 11) 1959. 2. Frohlich, E. D., and Freis, E. D.: M. Ann. District of Columbia 28:419 (Aug.) 1959. 3. Richardson, D. W., and Wyso, E. M.: Virginia M. Month. 86:377 (July) 1959. 4. Bres, A. N., and Moyer, J. H.: J.A.M.A. 172:1041 (March 5) 1960. 5. Page, I. H.: Postgrad. Med. 27:448 (April) 1960. 6. Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Paper presented at a Symposium on Guamethidine (tsmelin), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 7. Leishman, A. W. D., Matthews, H. L., and Smith, A. J.: Lancet 2:1044 (Dec. 12) 1959. References: 8. Brest, A. N., Duarte, C., Giantz, G., and Moyer, J. H.: Current Therap. Res. 2:17 (Jan.) 1960. 9. Maxwell, R. A., Mull, R. P., and Plummer, A. J.: Experientia 15:267 (July 15) 1959. 10. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. L.: Pharmacol. & Exper: Therap. 128:22 (Jan.) 1960. II. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. L.: Pharmacologist 1:69 (Fall) 1959. 12. Sheppard, H., and Zimmerman, J.: Pharmacologist 1:69 (Fall) 1959.

# near-normal levels in 80 to 90% of cases3

RESULTS: "All patients showed definite reduction in blood pressure coincident with administration of [Ismelin]. In most of the subjects [15] standing blood pressure could be maintained near normal levels."<sup>3</sup>

"Side-effects encountered . . . have indeed been minimal..."4 Brest and Moyer4 state: "Side-effects [of Ismelin] encountered to date have indeed been minimal, with mild diarrhea as the only significant complaint even when large daily doses (450 mg.) of the drug are administered. No evidence of toxic action of the drug has been encountered thus far." Page5 observes: "...Guanethidine [Ismelin] has the advantage [over ganglionic blockers] in that it is much easier to handle and does not produce nearly as much dose sensitivity. Too much of a ganglion-blocking agent will really 'clobber' the patient; with Guanethidine, there is much more leeway." Kirkendall and co-workers6 report: "Guanethidine has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy." Leishman and associates? conclude: "The capacity of guanethidine to reduce the bloodpressure of hypertensive patients





#### Ismelin Increases Arteriole Caliber

Ismelin represents a new principle in the treatment of high blood pressure: It acts at the nervearteriole junction where it apparently opposes the release and/or distribution of the pressor substance, norepinephrine. Ismelin is not a ganglionic blocker.

■ BEFORE ISMELIN: Photo shows normal arteriole in rat mesentery. (100x)

AFTER ISMELIN: Ismelin has blocked the constricting influence of norepinephrine. Arteriolar caliber has significantly increased, while an adjacent capillary has filled. (100x)

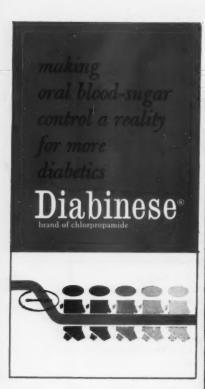
Because it acts at the nervearteriole junction—with no demonstrable central or ganglion blocking effect—Ismelin produces a clear-cut antihypertensive response in a high percentage of cases.

without symptoms of parasympathetic blockade is consistent with a mechanism of selective sympathetic-nerve inhibition..."

For complete information on precautions, dosage, and side effects, write to Medical Service Division, CIBA, Summit, New Jersey.

Supplied: ISMELIN Tablets, 10 mg. (yellow, scored) and 25 mg. (white, scored); bottles of 100. /=207 Mg. ISMILIN® sulfate (guanethidine sulfate CERA)





IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, longlasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Average maintenance dosage is 100-500 mg, daily. For most patients the recommended starting dose is 250 mg, given once daily. Geriatric patients should be started on 100-125 mg, daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg, or less daily. Maintenance dosage above 750 mg, should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

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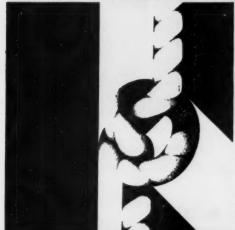


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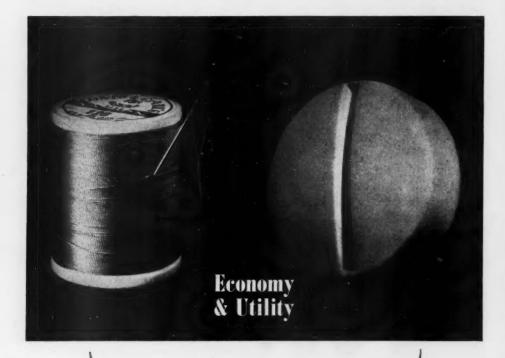
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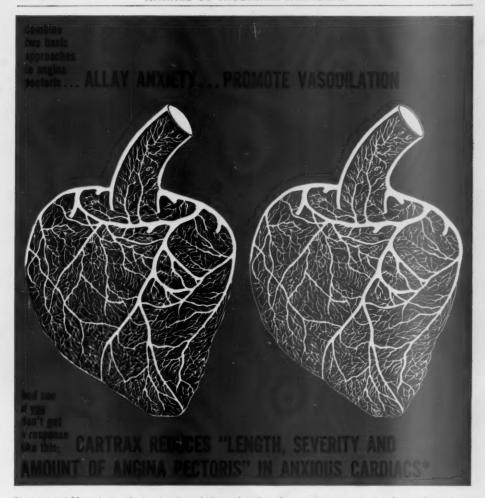
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\*Clark, T. E., in press.

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"Rock, J.; Garcia; C. R., & Pincue, G.: Am. J. Obas, & Gymes. 79:758, 1960.

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\*Simon, S. W.: Ann. Allergy 14:172-180 (March-April) 1956.

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1. Drugs of Choice 1960-1961, (Modell, W., Ed.), Mosby, St. Louis, 1960; p. 652.

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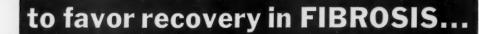
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(Pure Potassium Aminobenzoate, Glenwood)

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Evidence obtained from the observations of competent clinical investigators justifies the suggestion that this non-toxic drug may be found of great value wherever the pathological formation of fibrous tissue retards the patient's response to treatment.

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 Zarafonetis, C. J. D., and Horrax, T. M.: Treatment of Peyronie's Disease with POTABA, Journal of Urology, 81: 770-772 (June 1959).

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 Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 188:762, (Oct. 11) 1958.



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#### References:

t. Segal, M. S., and Durrino, M. J.: Chronic Bulmonary Emphysims. New York, Grune & Stratton, 1953, p. 59. S. Farber, S. H., and Wrison, R. H. L.: Ann. Int. Med. 50:1241, 1959. s. Borach, A. L., and Cromeell, H. A.: Med. Clin. No. America, May 1940, p. 621. 4. Bickerman, H. A., and Berech, A. L.; Drugs of Choice, 1960-1961 (W. Modell, etc.). St. Leuis, The C. V. Mosby Co., 1960, p. 524

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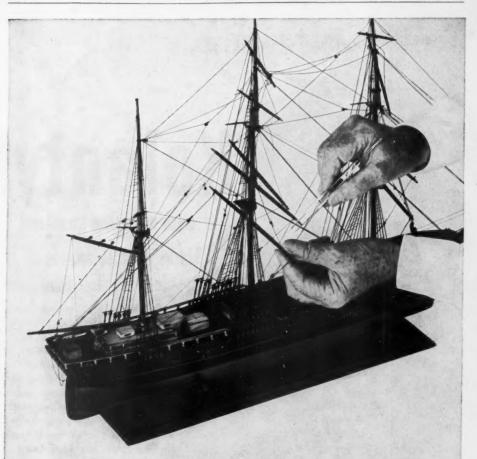
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- 1. Schwab, R. S. and England, A. C.: J. Chron. Dis. 8:488 (Oct.) 1958.
- 2. Schwab, R. S.: Geriatrics 14:545 (Sept.) 1959.
- 3. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb. 4) 1956.

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Kestler, O.: Conservative Management of "Low Back Syndrome", J.A.M.A. 172: 2039 (April 30) 1960.

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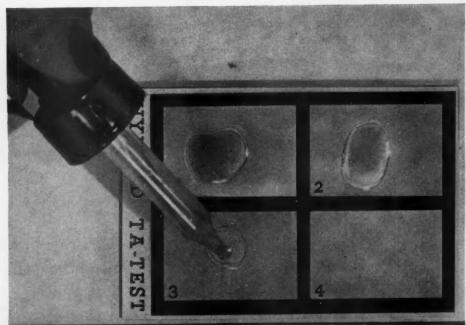
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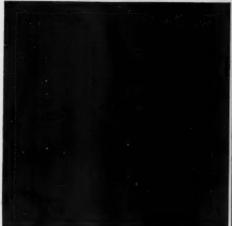
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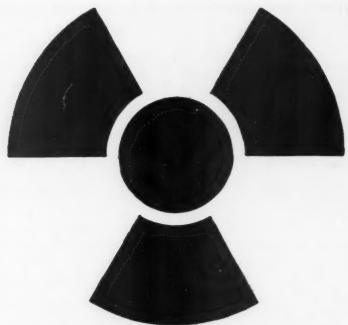


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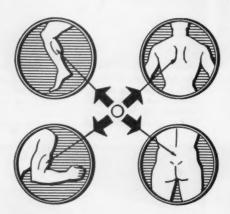
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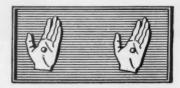
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1. Griffith, R. S.: Comparison of Antibiotic Activity in Sera Following the Administration of Three Different Penicillins, Antibiotic Med. & Clin. Therapy, 7: No. 2 (February), 1960.

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